DISSERTATION

ON

RISK FACTORS FOR DISTAL SYMMETRIC PERIPHERAL NEUROPATHY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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CERTIFICATE

This is to certify that dissertation entitled RISK FACTORS FOR DISTAL SYMMETRIC PERIPHERAL NEUROPATHY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS is the bonafide record of work done by **Dr.T.SIBI** in the Department of Internal Medicine, Thanjavur Medical College, Thanjavur during his Post Graduate Course from 2008 – 2011. This is submitted as partial fulfilment for the requirement of M.D. Degree Examinations – Branch I (Internal Medicine) to be held in APRIL 2011.

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I, **Dr.T.SIBI** solemnly declare that dissertation titled RISK FACTORS FOR DISTAL SYMMETRIC PERIPHERAL NEUROPATHY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS is a bonafide work done by me at Thanjavur Medical College Hospital during DEC 2008 – MAY 2010 under the guidance and supervision of Prof. DR. P.G. SANKARANARAYANAN M.D.,. The dissertation is submitted to **THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI, TAMILNADU** as partial fulfilment for the requirement of M.D. Degree Examinations – Branch I (General Medicine) to be held in April 2011.

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INDEX

LIST OF ABBREVIATIONS:

ABCD – Appropriate Blood pressure control in Diabetes

AGE - Advanced Glycation Endproducts

BMI - Body Mass Index

CAHD- Coronary Artery Heart Disease

CI – Confidence Interval

CIDP – Chronic Inflammatory Demyelinating Polyneuropathy

CVD – Cardio – vascular Disease

DCCT – Diabetes Control and Complications Trial

DM – Diabetes Mellitus

DPN – Diabetic Peripheral Neuropathy

DSPN – Distal Symmetric Peripheral Neuropathy

EDIC – Epidemiology of Diabetes Interventions and Complications

EMG – Electro - myogram

FBS – Fasting Blood Sugar

FPG – Fasting Plasma Glucose

HDL – High Density Lipoprotein

ICAM – Inter – Cellular Adhesion Molecule

IDDM – Insulin Dependent Diabetes Mellitus

LDL – Low Density Lipoprotein

MFD – Motor Fibre Density

MGUS – Monoclonal Gammopathy of Unknown Significance

MNSI – Michigan Neuropathic Screening Instrument

NCV – Nerve Conduction Velocity

NIDDM – Non – Insulin Dependent Diabetes Mellitus

NISLL – Nerve Impairment Score of Lower Limbs

NMDA - N-methyl D-aspartate

NNT – Number Needed to Treat

NTSS – Neuropathy Total Symptoms Score

OGTT – Oral Glucose Tolerance Test

PGP – Protein Gene Product

PN – Peripheral Neuropathy

PKC – Protein Kinase C

QAFT – Quantitative Autonomic Function Testing

QST – Quantitative Sensory Testing

T1DM – Type 1 Diabetes Mellitus

T2DM – Type 2 DiabetesMellitus

TGF – Transforming Growth Factor

TrkA – Neurotrophic Tyrosine Kinase – 1 Protein

UAE – Urine Albumin Excretion

UKPDS – United Kingdom Prospective Diabetes Complications Study

INTRODUCTION:

Diabetes is the leading cause of neuropathy in the Western world, and neuropathy is the most common complication and greatest source of morbidity and mortality in diabetes patients.[1] Peripheral neuropathy is the most common chronic complication of DM and can involve any peripheral nerve. It is a major cause of morbidity among patients with DM [2]. The prevalence and pattern of PN vary from country to country, from as low as 1.5% to as high as 100% in patients with type 2 diabetes [3-8] depending on the differences in screening approaches, diagnostic criteria and the study population. The neuropathy may be silent and go undetected. Up to 7.5% of patients with type 2 diabetes have clinical neuropathy at the time of diagnosis. This rate increases to 50% among patients with diabetes who have had diabetes for 25 years.[8].However, epidemiological studies of the impact of PN on type 2 diabetes in developing countries are scarce.

DN is a set of clinical syndromes that affect distinct regions of the nervous system, singly or combined. It may be silent and go undetected, while exercising its ravages or it may present with clinical symptoms and signs that although nonspecific and insidious with slow progression but also mimic those seen in many other diseases. It is, therefore, diagnosed by exclusion. Neurologic complications occur equally in type 1 and type 2 diabetes mellitus and additionally in various forms of acquired diabetes. . Progression of DN is related to glycemic control in both type 1 and type 2 diabetes. Sensory and autonomic neuropathies generally progress, while mononeuropathies, radiculopathies, and acute painful neuropathies, although symptoms are severe, are short-lived and tend to recover.

With improvement in treatment, the prevalence of type1 and type2 DM is likely to increase, as more individuals will live longer. Recent reports have concluded that if the aetiology is hyperglycemia, it's reversible on treatment. The study of risk factors for development of

diabetic peripheral neuropathy has revealed that increased age, longer duration of diabetes and poor glycemic control were significant risk factors [9].The National diabetes information clearing house ,has estimated that 50% of the diabetics have some form of neuropathy among the people who have had the disease for at least 25years[10]With linear increase in prevalence of neuropathy, it is therefore pertinent to look at the risk determinants of diabetic neuropathy as this will improve diabetes care. The present study aims at identifying the risk factors of diabetic neuropathy.

AIMS AND OBJECTIVES:

The objective of the study is to identify the risk factors associated with distal symmetrical peripheral neuropathy in type 2 diabetes mellitus patients who are attending diabetology out patient department in Thanjavur Medical College Hospital.

REVIEW OF LITERATURE:

The worldwide prevalence of DM has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 177 million in 2000. Based on current trends, >360 million individuals will have diabetes by the year 2030. Although the prevalence of both type 1 and type 2 DM is increasing worldwide, the prevalence of type 2 DM is rising much more rapidly because of increasing obesity and reduced activity levels as countries become more industrialized. This is true in most countries, and 6 of the top 10 countries with the highest rates are in Asia. DM increases with aging. The prevalence is similar in men and women throughout most age ranges but is slightly greater in men >60 years.

Diabetes is a major cause of mortality, but several studies indicate that diabetes is likely underreported as a cause of death. A recent estimate suggested that diabetes was the fifth leading cause of death worldwide and was responsible for almost 3 million deaths annually

The National Diabetes Data Group and World Health Organization have issued diagnostic criteria for DM based on the following premises:

(1) The spectrum of fasting plasma glucose (FPG) and the response to an oral glucose load (OGTT—oral glucose tolerance test) varies among normal individuals, and

(2) DM is defined as the level of glycemia at which diabetes-specific complications occur rather than on deviations from a population-based mean

Criteria for the Diagnosis of Diabetes Mellitus
• Symptoms of diabetes plus random blood glucose concentration 11.1 mmol/L (200 mg/dL) *or* • Fasting plasma glucose 7.0 mmol/L (126 mg/dL) *or* • Two-hour plasma glucose 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test

The chronic complications of DM affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease. Chronic complications can be divided into vascular and nonvascular complications

VASCULAR

MICROVASCULAR

Eye disease

Retinopathy

Macular edema

Neuropathy

Sensory and motor (nonproliferative/proliferative)

Autonomic

Nephropathy

MACROVASCULAR

Coronary artery disease

Peripheral arterial disease

Cerebrovascular disease

Other

Gastrointestinal (gastroparesis, diarrhea)

Genitourinary (uropathy/sexual dysfunction)

Dermatologic

Infectious

Cataracts

Glaucoma

Periodontal disease

The risk of chronic complications increases as a function of the duration of hyperglycemia; they usually become apparent in the second decade of hyperglycemia. Since type 2 DM often has a long asymptomatic period of hyperglycemia, many individuals with type 2 DM have complications at the time of diagnosis.

The microvascular complications of both type 1 and type 2 DM result from chronic hyperglycemia. Large, randomized clinical trials of individuals with type 1 or type 2 DM have conclusively demonstrated that a reduction in chronic hyperglycemia prevents or delays retinopathy, neuropathy, and nephropathy. Other incompletely defined factors may modulate the development of complications. Many of these patients have glycemic control that is indistinguishable from those who develop microvascular complications, suggesting that there is a genetic susceptibility for developing particular complications.

Evidence implicating a causative role for chronic hyperglycemia in the development of macrovascular complications is less conclusive. However, coronary heart disease events and mortality are two to four times greater in patients with type 2 DM. These events correlate with fasting and postprandial plasma glucose levels as well as with the A1C. Other factors (dyslipidemia and hypertension) also play important roles in macrovascular complications.

DIABETIC NEUROPATHIES

Diabetic neuropathies are a heterogeneous group of disorders and present a wide range of abnormalities. They are among the most common long-term complications of diabetes and are a significant source of morbidity and mortality.[12,13] Estimates of the prevalence of neuropathy vary substantially, depending on specific diagnostic criteria.[14,15] In the United States, prevalence estimates have ranged from 5% to 100%.[12,14,15–17]

In Pirart's classic study of a cohort of 4400 patients, prevalence was found to reach approximately 45% after 25 years.[18] Furthermore, it is now evident that neuropathy can occur with impaired glucose tolerance[19] and with the metabolic syndrome in the absence of hyperglycemia.[20] It is the most common form of neuropathy in the developed countries of the world, accounts for more hospitalizations than all the other diabetic complications combined, and is responsible for 50% to 75% of nontrauma amputations.[16,17]

Diabetic peripheral neuropathy is also responsible for weakness and ataxia, with an estimated increase in likelihood of falling that is 15 times that of unaffected population.[21,22]

The true prevalence is not known and depends on the criteria and methods used to define neuropathy. Of patients attending a diabetes clinic, 25% volunteered symptoms, but 50% were found to have neuropathy after a simple clinical test such as the ankle jerk or vibration perception test. Almost 90% tested positive to sophisticated tests of autonomic function or peripheral sensation.[23] Neurologic complications occur equally in T1DM and T2DM and additionally in various forms of acquired diabetes.[15]Neuropathy increases the risk of amputation 1.7-fold, 12-fold if there is deformity (itself a consequence of neuropathy), and 36-fold if there is a history of previous ulceration.[24]

There are 86,000 amputations in the United States each year, one every 10 minutes, and neuropathy is the major contributor in 87% of cases.[13] Once autonomic neuropathy sets in, life can become quite dismal, and the mortality rate approximates 25% to 50% within 5 to 10 years.[25–28]

Classification

Diabetic neuropathy is not a single entity but a number of different syndromes with subclinical or clinical manifestations depending on the classes of nerve fibers involved. According to the San Antonio Convention,[29] the main groups of neurologic disturbance in diabetes mellitus include:

- Subclinical neuropathy, which is determined by abnormalities in electrodiagnostic and quantitative sensory testing
- Diffuse clinical neuropathy with distal symmetric sensorimotor and autonomic syndromes
- Focal syndromes

Subclinical neuropathy is diagnosed on the basis of abnormal electrodiagnostic tests with decreased nerve conduction velocity (NCV) or decreased amplitudes; abnormal quantitative sensory tests (QST) for vibration, tactile, thermal warming, and cooling thresholds; and quantitative autonomic function tests (QAFT) revealing diminished heart rate variation with deep breathing, Valsalva maneuver, and postural testing.

Natural History

The natural history of neuropathies separates them into two very distinct entities, namely those that progress gradually with increasing duration of diabetes and those that remit, usually completely. Sensory and autonomic neuropathies generally progress, and mononeuropathies, radiculopathies, and acute painful neuropathies, although symptoms are severe, are short-lived, and patients tend to recover.[30]

Progression of neuropathy is related to glycemic control in both T1DM and T2DM.[31,32] In T2DM, slowing of NCVs may be one of the earliest neuropathic abnormalities and often is present even at diagnosis.[33] After diagnosis, slowing of NCV generally progresses at a steady rate of approximately 1 m/sec per year, and the level of impairment is positively correlated with duration of diabetes. In a long-term follow-up study of T2DM patients,[34] electrophysiologic abnormalities in the lower limb increased from 8% at baseline to 42% after 10 years.

It has always been assumed that diabetes affects the longest fibers first—hence, the increased predisposition in taller persons.[35]

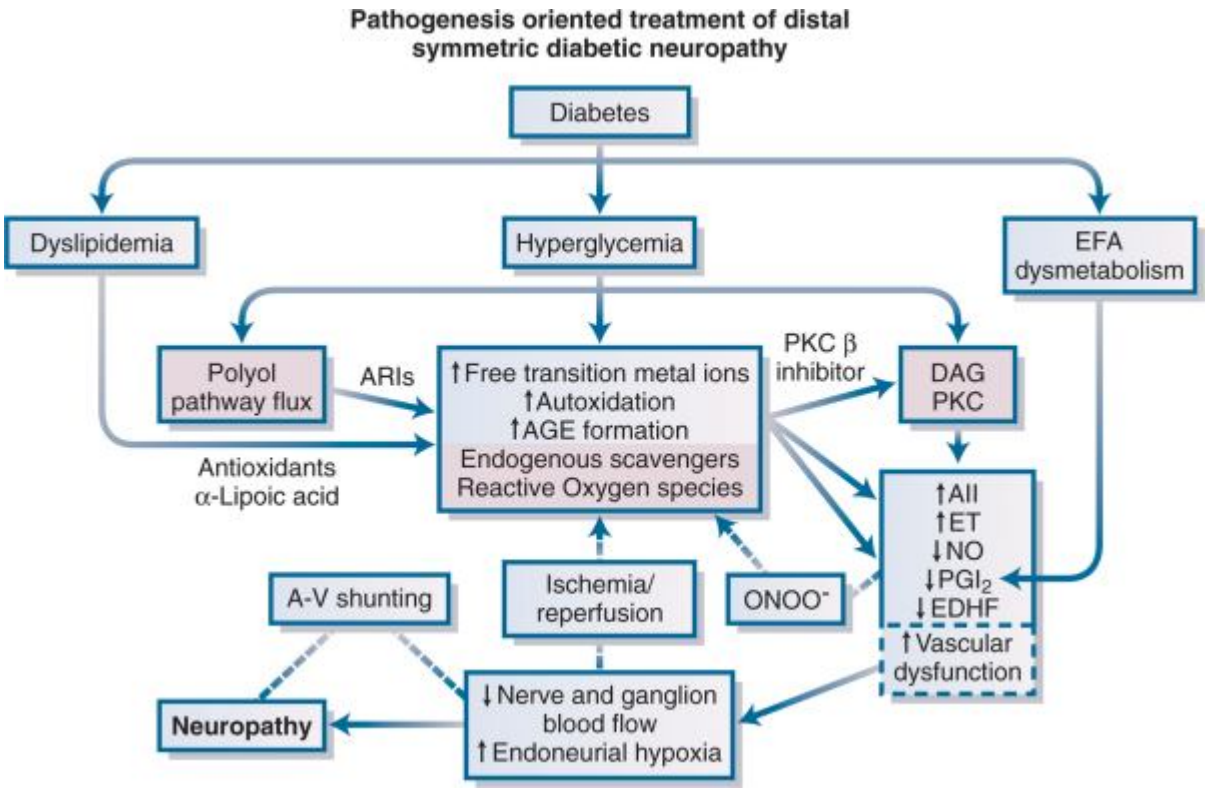
Now it seems that small-fiber involvement can herald the onset of neuropathy and even diabetes. Small-fiber function is not detectable using standard electrophysiology and requires measurement of sensory, neurovascular, and autonomic thresholds and cutaneous nerve fiber density.[20,36–38] There are few data on the longitudinal trends in small-fiber dysfunction, although it appears that the nerve fiber loss in prediabetic neuropathy might respond to lifestyle changes.[39]

Much remains to be learned of the natural history of diabetic autonomic neuropathy. Karamitsos and colleagues[40] have reported that the progression of diabetic autonomic neuropathy is significant during the 2 years subsequent to its discovery. The mortality rate for diabetic autonomic neuropathy has been estimated to be 44% within 2.5 years of diagnosing symptomatic autonomic neuropathy.[25]A meta-analysis[41] revealed that the mortality rate after 5.8 years of diabetes with symptomatic autonomic neuropathy was 29%. In a meta-analysis of 12 published studies, reduced cardiovascular function as measured by heart rate variability was shown to be associated with an increased risk of silent myocardial infarction.[28]The relative risk of mortality from 15 studies (N=2900;

95% CI) was increased in patients with cardiac autonomic neuropathy by 2.14 (CI 1.83-2.51).[28]

Pathophysiology

The factors leading to the development of peripheral neuropathy in diabetes are not understood completely, and multiple hypotheses have been advanced. It is generally accepted to be a multifactorial process. Important contributing biochemical mechanisms in the development of the more common symmetrical forms of diabetic polyneuropathy likely include the following:



Management aimed at pathogenic mechanisms. AII, angiotensin II; A-V, arteriovenous; EDHF, endothelium-derived hyperpolarizing factor; EFA, essential fatty acid; ET, endothelin; NO, nitric oxide; PGI_2, prostaglandin I_2.
(Adapted from Vinik A, Mehrabyan A. Diabetic neuropathies. Med Clin North Am 2004;88(4):947-999.)

Polyol pathway

Hyperglycemia causes increased levels of intracellular glucose in nerves, leading to saturation of the normal glycolytic pathway. Extra glucose is shunted into the polyol pathway and converted to sorbitol and fructose by the enzymes aldose reductase and sorbitol dehydrogenase. Accumulation of sorbitol and fructose lead to reduced nerve myoinositol, decreased membrane Na^+/K^+ -ATPase activity, impaired axonal transport, and structural breakdown of nerves, causing abnormal action potential propagation. This is the rationale for the use of aldose reductase inhibitors to improve nerve conduction.[42]

Advanced glycation end products (AGE)

The nonenzymatic reaction of excess glucose with proteins, nucleotides, and lipids results in advance glycation end products that may have a role in disrupting neuronal integrity and repair mechanisms through interference with nerve cell metabolism and axonal transport.[43]

Oxidative stress

The increased production of free radicals in diabetes may be detrimental via several mechanisms that are not fully understood. These include direct damage to blood vessels leading to nerve ischemia and facilitation of AGE reactions. Despite the incomplete understanding of these processes, use of the antioxidant alpha lipoic acid may hold promise for improving neuropathic symptoms.[44]

Clinical Presentation

An international consensus meeting on the outpatient diagnosis and management of diabetic neuropathy agreed that a simple definition of diabetic neuropathy was “the

presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes."[29]

The importance of excluding nondiabetic causes was emphasized in the Rochester Diabetic Neuropathy Study, in which up to 10% of peripheral neuropathy in diabetic patients was deemed to be of nondiabetic etiology.[15]

A more detailed definition of neuropathy had previously been agreed on at the San Antonio Consensus Conference: "Diabetic neuropathy is a descriptive term meaning a demonstrable disorder, either clinically evident or sub-clinical, that occurs in the setting of diabetes mellitus without other causes for peripheral neuropathy. The neuropathic disorder includes manifestations in the somatic and/or autonomic parts of the peripheral nervous system."[29]

In the goal A_{1c} study,[45] identification of the absence of neuropathy in 7000 patients was fairly adequate but was only accurate in the presence of mild neuropathy one third of the time, and it reached 75% only if neuropathy was severe. Clearly there is a need for education of the means whereby neuropathy may be diagnosed.

Focal Neuropathies

Mononeuropathies occur primarily in the older population. Their onset is generally acute and associated with pain, and their course is self-limiting, resolving within 6 to 8 weeks. Mononeuropathies result from vascular obstruction after which adjacent neuronal fascicles take over the function of those infarcted by the clot.[46] Common entrapment sites in diabetic patients involve median, ulnar, and radial nerves; femoral nerves, lateral cutaneous nerves of the thigh, and peroneal nerves; and the medial and lateral plantar nerves.

Carpal tunnel syndrome occurs three times as often in persons with diabetes compared with a normal, healthy population,[47,48] and its increased prevalence in diabetes may be related to

diabetic cheiroarthropathy,[49] repeated undetected trauma, metabolic changes, or accumulation of fluid or edema within the confined space of the carpal tunnel.[50]

DIFFUSE NEUROPATHIES

Proximal Motor Neuropathies

The condition has a number of synonyms; proximal neuropathy, femoral neuropathy, diabetic amyotrophy, and diabetic neuropathic cachexia.

The condition is now recognized as secondary to a variety of causes that are unrelated to diabetes but that have a greater incidence in patients with diabetes than in the general population. This includes patients with chronic inflammatory demyelinating polyneuropathy (CIDP), monoclonal gammopathy, circulating GM1 antibodies and antibodies to neuronal cells, and inflammatory vasculitis.[51,52] However, immune-mediated neuropathy can resolve within days on immunotherapy.

In the classic form of diabetic amyotrophy, axonal loss is the predominant process, and the condition coexists with DSPN.[53] Electrophysiologic evaluation reveals lumbosacral plexopathy.[54]

If demyelination predominates and the motor deficit affects proximal and distal muscle groups, the diagnosis of CIDP, monoclonal gammopathy of unknown significance (MGUS), and vasculitis should be considered.[55,56] It seems probable that these conditions occur more commonly in people with diabetes.[57,58] Sharma examined more than 1000 patients with neurologic disorders and found that CIDP was 11 times more common among their diabetic than the nondiabetic population.[58]

Distal Symmetric Polyneuropathy

Distal symmetric polyneuropathy (DSPN) is the most common and widely recognized form of diabetic neuropathy. The onset is usually insidious but occasionally is acute, following stress or initiation of therapy for diabetes. DSPN may be either sensory or motor and can involve small fibers, large fibers, or both.[59]

Small nerve fiber dysfunction usually occurs early and often is present without objective signs or electrophysiologic evidence of nerve damage.[60] It is manifested early with symptoms of pain and hyperalgesia in the lower limbs, followed by a loss of thermal sensitivity and reduced light touch and pinprick sensation.[50]

There is now evidence that DSPN may be accompanied by loss of cutaneous nerve fibers that stain positive for the neuronal antigen panaxonal marker protein gene product 9.5 (PGP 9.5)[61] and by impaired neurovascular blood flow.[62] The importance of the skin biopsy as a diagnostic tool for diabetic peripheral neuropathy is increasingly being recognized.[20,36,63,64] This technique quantitates small epidermal nerve fibers through antibody staining of PGP 9.5.[65,66,67] Though minimally invasive (3-mm–diameter punch biopsies), it enables a direct study of small fibers that cannot be evaluated by NCV studies.

Small-Fiber Neuropathies

Symptoms are prominent in small-fiber neuropathies. Pain is of the C-fiber type. It is burning and superficial and is associated with allodynia (interpretation of all stimuli as painful). Patients have defective autonomic function with decreased sweating, dry skin, impaired vasomotion and blood flow, and cold feet. There are abnormalities in thresholds for warm thermal perception, neurovascular function, pain, quantitative sudorimetry, and

quantitative autonomic function tests. However, there is remarkable intactness of reflexes and motor strength.

Clinical diagnosis is by reduced sensitivity to 1.0-g Semmes-Weinstein monofilament and pricking sensation using the Waardenberg wheel or similar instrument. These neuropathies are electrophysiologically silent.

Large-Fiber Neuropathies

Large fibers subserve motor function, vibration perception, position sense, and cold thermal perception. They tend to be affected first because of their length and the tendency in diabetes for nerves to die back. Because they are myelinated, they are the fibers represented in the EMG, and subclinical abnormalities in nerve function are readily detected.

Clinical Presentation:

Signs and symptoms of larg-fiber neuropathy include impaired vibration perception (often the first objective evidence) and position sense, depressed tendon reflexes, and sensory ataxia (waddling like a duck. Signs in the distal lower extremities include wasting of the small muscles of the feet, with hammertoes (intrinsic minus feet and hands) and weakness of the feet; shortening of the Achilles tendon with pes equinus, and increased blood flow (hot foot). Patients also have weakness in the hands.

Most patients with DSPN, however, have a mixed variety of neuropathy, with both large and small nerve fiber damage. In the case of DSPN, a glove-and-stocking distribution of sensory loss is almost universal.[50] Early in the course of the neuropathic process, multifocal sensory loss also might be found. In some patients, severe distal muscle

weakness can accompany the sensory loss, resulting in an inability to stand on the toes or heels.

Diagnosis of Peripheral Neuropathy:

The diagnosis of diabetic neuropathy rests heavily on a careful history, for which a number of questionnaires have been developed by Young and colleagues,[14] Dyck,[68] Vinik,[69] and others.[70,71]

The initial neurologic evaluation should be directed toward detecting the specific part of the nervous system affected by diabetes. Bedside neurologic examination is quick and easy but provides nominal or ordinal measures and contains substantial inter-and intraindividual variation.

The 1988 San Antonio conference on diabetic neuropathy and the 1992 conference of the American Academy of Neurology[29] recommended that at least one parameter from each of the following five categories are measured to classify diabetic neuropathy: symptom profiles, neurologic examination, QST, nerve conduction study, and autonomic function testing. A number of simple symptom screening questionnaires are available to record symptom quality and severity.

A simplified neuropathy symptom score that was used in the European prevalence studies could also be useful in clinical practice.[14,72]

The Michigan Neuropathy Screening Instrument (MNSI) is a 15-item questionnaire that can be administered to patients as a screening tool for neuropathy.[71] Other similar

symptom-scoring systems have also been described, such as the nerve impairment score of the lower limbs (NIS-LL).[73]

Simple visual analogue or verbal descriptive scales may be used to follow patients' responses to treatment of their neuropathic symptoms.[74,75]

An international group of experts in diabetic neuropathy held a consensus meeting to develop guidelines for managing diabetic peripheral neuropathy by the practicing clinician.[29] This clinical staging is in general agreement with that proposed by Dyck[76] for use in both clinical practice and epidemiologic studies or controlled clinical trials.

The clinical *no neuropathy* is equivalent to Dyck's N0 (no objective evidence of diabetic neuropathy) or N1a (no symptoms or signs but neuropathic test abnormalities). *Clinical neuropathy* is equivalent to N1b (test abnormalities plus neuropathic impairment on neurologic exam), N2a (symptoms, signs, and test abnormalities), and N2b (N2a plus significant ankle dorsiflexor weakness). *Late complications* is equivalent to Dyck N3 (disabling polyneuropathy).

Peripheral Testing Devices

The most widely used device in clinical practice is the Semmes-Weinstein monofilament.[77–79] The filament assesses pressure perception when gentle pressure is applied to the handle sufficient to buckle the nylon filament. It is also referred to as the 5.07 monofilament because, during calibration, the filaments are calibrated to exert a force measured in grams that is 10 times the log of the force exerted at the tip: hence 5.07 exerts 10 g force. A number of cross-sectional studies have assessed the sensitivity of the 10-g monofilament to identify feet at risk for ulceration. Sensitivities vary from 86% to 100%,[80,81] although there is no consensus as to how many sites should be tested.

The commonest algorithm recommends four sites per foot, generally the hallux and the first, third, and fifth metatarsal heads.[78] However, there is little advantage to multiple site assessments.[82] There is also no universal agreement about what constitutes an abnormal result (one, two, three, or four abnormal results from the sites tested). Despite these problems, the 10-g monofilament is widely used to clinically assess risk of foot ulceration.

The graduated Rydel-Seifer tuning fork is used in some centers to assess neuropathy.[83,84] Liniger and colleagues reported that results with this instrument correlated well with other QST measures.[83]

The tactile circumferential discriminator assesses the perception of calibrated change in the circumference of a probe (a variation of two-point discrimination).[85] Vileikyte and coworkers[86] reported a 100% sensitivity in identifying patients at risk for foot ulceration.[86]

Neuropen is a clinical device that assesses pain using a pin (Neurotip) at one end of the pen and a 10-g monofilament at the other end. This was shown to be a sensitive device for assessing nerve function when compared to the simplified neuropathy disability score.[620]

Biopsy

Biopsy of nerve tissue may be helpful for excluding other causes of neuropathy and in determining predominant pathologic changes in patients with complex clinical findings as a means of dictating choice of treatment.[53,87] Skin biopsy has some clinical advantages in diagnosing small-fiber neuropathies by quantification of PGP9.5 when all other measures are negative.[36,88]

Nerve Conduction Studies

Whole nerve electrophysiologic procedures (e.g., NCV, F-waves, sensory amplitudes, motor amplitudes) have emerged as important methods of tracing the onset and progression of peripheral neuropathy.[89]

These are objective, parametric, noninvasive and highly reliable measures. However, standard procedures, such as maximal NCV, reflect only a limited aspect of neural activity, and then only in a small subset of large-diameter and heavily myelinated axons. Even in large-diameter fibers, NCV is insensitive to many pathologic changes known to be associated with peripheral neuropathy.

However, a key role for electrophysiologic assessment is to rule out other causes of neuropathy or to identify neuropathies superimposed on peripheral neuropathy.

NCV is only gradually diminished by peripheral neuropathy, with estimates of a loss of approximately 0.5 m/sec per year.[89]

In a 10-year natural history study of 133 patients with newly diagnosed T2DM, NCV deteriorated in all six nerve segments evaluated, but the largest deficit was 3.9 m/sec for the sural nerve (48.3 m/sec slowed to 44.4 m/sec); peroneal motor NCV was decreased by 3.0 m/sec over the same period.[34]

A similar slow rate of decline was demonstrated in the DCCT. A simple rule is that a decrease in HB A_{1c} of one percentage point improves conduction velocity about 1.3 m/sec.[90] There is, however, a strong correlation ($r = 0.74$; $P < 0.001$) between myelinated fiber density and whole nerve sural amplitude.[634]

Management:

Once neuropathy is diagnosed, therapy can then be instituted with the goal of both ameliorating symptoms and preventing the progression of neuropathy. Successful management of these syndromes must be geared to individual pathogenic processes.

Control of Hyperglycemia:

Pirart[18] followed 4400 diabetic patients over 25 years and showed an increase in prevalence of clinically detectable diabetic neuropathy from 12% of patients at the time of diagnosis of diabetes to almost 50% after 25 years. The highest prevalence occurred in the people with poorest diabetes control.

The DCCT Research Group[31] reported significant effects of intensive insulin therapy on prevention of neuropathy. The results of the DCCT study support the necessity for strict glycemic control, but the effect of insulin as a growth factor and immunomodulator, aside from its metabolic effects, must also be investigated.

In the UKPDS, control of blood glucose was associated with improvement in vibration perception.[91] In the Steno trial,[92] a reduction of the odds ratio for the development of autonomic neuropathy to 0.32 was reported. This was a stepwise, progressive study that involved treating T2DM patients with hypotensive drugs, including ACE inhibitors, calcium-channel antagonists, hypoglycemic agents, aspirin, hypolipidemic agents, and antioxidants. These findings argue strongly for the multifactorial nature of neuropathy and for the need to address the multiple metabolic abnormalities.

Pharmacologic Therapy:

Aldose Reductase Inhibitors:

Aldose reductase inhibitors (ARIs) reduce the flux of glucose through the polyol pathway, inhibiting tissue accumulation of sorbitol and fructose and preventing reduction of redox potentials.

In a placebo-controlled, double-blind study of tolrestat, 219 diabetic patients with symmetrical polyneuropathy, as defined by at least one pathologic cardiovascular reflex, were treated for 1 year.[92] Patients who received tolrestat showed significant improvement in autonomic function tests and in vibration perception, whereas placebo-treated patients showed deterioration in most of the parameters measured.[93]

There is a dose-dependent improvement in nerve fiber density, particularly small unmyelinated nerve fibers, in a 12 month study of zenarestat.[94] This was accompanied by an increase in NCV, although the changes in NCV occurred at a dose of the drug that did not change the nerve fiber density.[94] Impaired cardiac ejection fractions can be improved with zopolrestat.[95] Clinical improvement has been reported for fidarestat and epalrestat in Japan.[96,97]

α-Lipoic Acid:

Lipoic acid (1,2-dithiolane-3-pentanoic acid), a derivative of octanoic acid, is present in food and is also synthesized by the liver. It is a natural cofactor in the pyruvate dehydrogenase complex, where it binds acyl groups and transfers them from one part of the complex to another. α-Lipoic acid, which also known as thioctic acid, has generated considerable interest as a thiol-replenishing and redox-modulating agent. It has been shown to be effective in ameliorating the somatic and autonomic neuropathies in diabetes.[98–100]

γ-Linolenic Acid:

Linoleic acid, an essential fatty acid, is metabolized to dihomo-g-linolenic acid, which serves as an important constituent of neuronal membrane phospholipids and as a substrate for prostaglandin E formation, which appears to be important for preserving nerve blood flow. In diabetes, conversion of linoleic acid to γγlinolenic acid and subsequent metabolites is impaired, possibly contributing to the pathogenesis of diabetic neuropathy.[101]

Protein Kinase C-β Inhibition:

Neural vascular insufficiency has been proposed as a contributing factor to development of diabetic neuropathy.[102] PKC activation is a critical step in the pathway to diabetic microvascular complications[103] It is hyperactivated by hyperglycemia and disordered fatty acid metabolism, resulting in increased production of vasoconstrictive, angiogenic, and chemotactic cytokines including TGF-β, VEGF, endothelin, and ICAMs.

Preliminary results of a multinational randomized, double-blind, placebo-controlled phase II trial showed a statistically significant improvement in symptoms, measured by the Neuropathy Total Symptom Score 6 (NTSS-6), in ruboxistaurin-treated neuropathy groups as compared with placebo.[104] The drug was well tolerated and there were few adverse events.

Aminoguanidine:

Animal studies using aminoguanidine, an inhibitor of the formation of AGEs, show improvement in nerve conduction velocity in streptozotocin-induced diabetic neuropathy in rats. Controlled clinical trials to determine its efficacy in humans[105,106] have been

discontinued because of toxicity. There are, however, successors to aminoguanidine that hold promise for this approach.[107]

Neurotrophic Therapy:

In a 15-center double-blind, placebo-controlled study of the safety and efficacy of rhNGF in 250 subjects with symptomatic small-fiber neuropathy,[108] rhNGF improved the neurologic impairment score of the lower limbs and improved small nerve fiber function cooling threshold (Aδ-fibers) and the ability to perceive heat pain (C-fiber) compared with placebo. These results were consistent with the postulated actions of NGF on TrkA receptors present on small-fiber neurons.

Results of these NGF studies were presented at the ADA meetings in June 1999.[109] Regrettably, rhNGF was not found to have beneficial effects over placebo. The reason for this dichotomy has not been resolved, but this has somewhat dampened the enthusiasm for growth factor therapy of diabetic neuropathy.

Pain Control:

Control of pain constitutes one of the most difficult management issues in diabetic neuropathy. In essence, simple measures are tried first. If no distinction is made for pain syndromes, then the number needed to treat (NNT) to reduce pain by 50% is 1.4 for optimal-dose tricyclic antidepressants, 1.9 for dextromethorphan, 3.3 for carbamazepine, 3.4 for tramadol, 3.7 for gabapentin, 5.9 for capsaicin, 6.7 for selective serotonin reuptake inhibitors, and 10.0 for mexiletine.[110]

Insulin:

Continuous intravenous insulin infusion without resort to blood glucose lowering may be useful in these patients. A response with reduction of pain usually occurs within 48 hours,[111] and the insulin infusion can be discontinued. If this measure fails several medications are available that might abolish the pain.

Nerve Blocking:

Lidocaine given by slow infusion has been shown to provide relief of intractable pain for 3 to 21 days. If successful, therapy can be continued with oral mexiletine. These compounds target the pain caused by hyperexcitability of superficial free nerve endings.[112]

Tramadol and Dextromethorphan:

Tramadol was shown to be better than placebo in a randomized, controlled trial[113] of only 6 weeks' duration, but a subsequent follow-up study suggested that symptomatic relief could be maintained for at least 6 months.[114]Another spinal cord target for pain relief is the excitatory glutaminergic *N*-methyl-d-aspartate (NMDA) receptor. Blockade of NMDA receptors is believed to be one mechanism by which dextromethorphan exerts analgesic efficacy.[115]

Antidepressants:

Among the norepinephrine reuptake inhibitors, desipramine, amitriptyline, and imipramine have been shown to be of benefit.[116,117]

Selective serotonin reuptake inhibitors (SSRIs) that have been used for neuropathic pain are paroxetine, fluoxetine, sertraline, and citalopram.

Antiepileptic Drugs:

Anticonvulsants have stood the test of time in treatment of diabetic neuropathy.[118,119] Principal mechanisms of action include sodium channel blockade (felbamate, lamotrigine, oxcarbazepine, topiramate, zonisamide), potentiation of γ-aminobutyric acid (GABA) activity (tiagabine, topiramate), calcium-channel blockade (felbamate, lamotrigine, topiramate, zonisamide), antagonism of glutamate at NMDA receptors (felbamate) or α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) (felbamate, topiramate).[120]

Adjunct Management and Treatment of Complications:

Patients can benefit from high-intensity strength training by increasing muscle strength and improving coordination and balance, thus reducing fall and fracture risks.[121,122] In addition, options to prevent and correct foot deformities are available, including orthotics, surgery, and reconstruction.

Prevention:

Basic management of small-fiber neuropathies by the patient should be encouraged. These include foot protection and ulcer prevention by wearing padded socks; daily foot inspection using a mirror to examine the soles of the feet; selection of proper footwear; scrutiny of shoes for the presence of foreign objects that lodge themselves in closed shoes; and avoidance of sun-heated surfaces, hot bathwater, and sleeping with feet in front of fireplaces or heaters.

Stimulation:

Transcutaneous nerve stimulation (electrotherapy) occasionally is helpful and certainly represents one of the more benign therapies for painful neuropathy.[123] However, this cannot be generally recommended except in very resistant cases because it is invasive, expensive, and unproven in controlled studies.

Autonomic Neuropathies:

Diabetic autonomic neuropathy can cause dysfunction of every part of the body. Diabetic autonomic neuropathy often goes completely unrecognized by patient and physician alike because of its insidious onset and protean multiple organ involvement. The organ systems that most often exhibit prominent clinical autonomic signs and symptoms in diabetes include the ocular pupil, sweat glands, genitourinary system, gastrointestinal system, adrenal medullary system, and cardiovascular system.

DIAGNOSTIC TESTS OF CARDIOVASCULAR AUTONOMIC NEUROPATHY

RESTING HEART RATE
Rate >100 beats/min is abnormal.
BEAT-TO-BEAT HEART RATE VARIATION[*]
With the patient at rest and supine (no overnight coffee or hypoglycemic episodes), breathing 6 breaths/min, heart rate monitored by ECG or Anscore device, a difference in heart rate of >15 beats/min is normal and <10 beats/min is abnormal, R-R inspiration to R-R expiration >1.17. All indices of HRV are age-dependent.[†]
HEART RATE RESPONSE TO STANDING[*]
During continuous ECG monitoring, the R-R interval is measured at beats 15 and 30 after standing. Normally, a tachycardia is followed by reflex bradycardia. The 30 : 15 ratio is normally >1.03.
HEART RATE RESPONSE TO VALSALVA MANEUVER[*]
The subject forcibly exhales into the mouthpiece of a manometer to 40 mm Hg for 15 seconds during ECG monitoring. Healthy subjects develop tachycardia and peripheral vasoconstriction during strain and an overshoot bradycardia and rise in blood pressure with release. The ratio of longest R-R shortest R-R should be >1.2.
SYSTOLIC BLOOD PRESSURE RESPONSE TO STANDING
Systolic blood pressure is measured in the supine subject. The patient stands and the systolic blood pressure is measured after 2 min. Normal response is a fall of <10 mm Hg, borderline is a fall of 10-29 mm Hg, and abnormal is a fall of >30 mm Hg with symptoms.
DIASTOLIC BLOOD PRESSURE RESPONSE TO ISOMETRIC EXERCISE
The subject squeezes a handgrip dynamometer to establish a maximum. Grip is then squeezed at 30% maximum for 5 min. The normal response for diastolic blood pressure is a rise of >16 mm Hg in the other arm.
ECG QT/QTC INTERVALS
The QTc (corrected QT intevval on EKG) should be <440 ms.
SPECTRAL ANALYSIS

HF peak ↓ (parasympathetic dysfunction) LF peak ↓ (sympathetic dysfunction) LH/HF ratio ↓ (sympathetic imbalance) VLF peak ↓ (sympathetic dysfunction)
NEUROVASCULAR FLOW
Noninvasive laser Doppler measures peripheral sympathetic responses to nociception.

ECG, electrocardiogram; HF, high frequency; HRV, heart rate variation; LF, low frequency; VLF, very low frequency.

* These can now be performed quickly (<15 min) in the practitioner's office, with a central reference laboratory providing quality control and normative values. These are now readily available in most cardiologist's practice.

† Lowest normal value of E/I ratio: Age 20-24 yr: 1.17; 25-29 yr: 1.15; 30-34 yr: 1.13; 35-30 yr: 1.12; 40-44 yr: 1.10; 45-49 yr: 1.08; 50-54 yr: 1.07; 55-59 yr: 1.06; 60-64 yr: 1.04; 65-69 yr: 1.03; 70-75 yr: 1.02.

Management

Postural Hypotension

The syndrome of postural hypotension is posture-related dizziness and syncope. Patients who have T2DM and orthostatic hypotension are hypovolemic and have sympathoadrenal insufficiency; both factors contribute to the pathogenesis of orthostatic hypotension.[124]

Supportive Garments

Whenever possible, attempts should be made to increase venous return from the periphery using total body stockingsPatients should be instructed to put these garments on while lying down and to not remove them until returning to the supine position.

Drug Therapy

Some patients with postural hypotension benefit from treatment with 9-fluorohydrocortisone. Metoclopromide may be helpful in patients with dopamine excess or increased sensitivity to dopaminergic stimulation. Patients with α_2-adrenergic receptor excess might respond to the α_2-antagonist yohimbine. Those few patients in whom β-receptors are increased may be helped with propranolol. α_2-Adrenergic receptor deficiency can be treated with the α_2-agonist clonidine, which in this setting can paradoxically increase BP.

MATERIALS AND METHODS :

The study was conducted in Department of General Medicine, Thanjavur Medical College from December 2008 to May 2010.

It was a cross-sectional study involving one hundred diabetic patients attending the diabetic clinics. They were chosen by stratified randomized sampling. They were categorized into two groups of 50 each based on comprehensive neurological examination (Michigan Neuropathic Diabetic Scoring – MNDS and monofilament testing).

Group 1 included type 2 diabetes mellitus patients without peripheral neuropathy.

Group 2 included type 2 diabetes mellitus patients with peripheral neuropathy.

MNDS gives the score in the range of 0 – 8, based on evaluation of 4 different factors in each link. These factors are appearance of foot (dry skin, callus, deformity, fissure, and infection), presence of ulcer, Achilles tendon reflex, and vibration perception of the great toe with 128Hz tuning fork. A neuropathic foot scores 3 or higher, while a normal foot scores 2.5 or lower. This scoring system has the sensitivity and specificity of 95%.

Neuropathy was also defined as the loss of protective sensation determined through application of the 10-g Semmes-Weinstein monofilament wire system.

INCLUSION CRITERIA:

- Type 2 diabetics between 20 and 80 years of age.
- Duration of diabetes more than 4 years

EXCLUSION CRITERIA

- Serum creatinine more than 2 mg/dl
- Pregnant women
- DM of specific etiology
- Diabetic emergencies
- Medications known to cause peripheral neuropathy
- Alcoholism
- Hansen's disease
- AIDS
- Hypothyroidism
- Stroke
- B12 deficiency
- Loss of dorsalis pedis pulsation

PROCEDURE:

After written informed consent, detailed information on patient's age, sex, duration of diabetes, presence of hypertension, Coronary artery disease (CAD), smoking, were obtained. Body mass index and presence or absence of postural hypotension was recorded. The following investigations were carried out: HbA1c(%), fasting blood sugar, post prandial blood sugar, lipid profile, spot test for albuminuria and micro-albuminuria, blood urea and serum creatinine, hemoglobin (gm/dl).

Parameters studied:

- Duration of diabetes
- Glycemic control
- Lipid profile
- Albuminuria
- Micro-albuminuria
- Systemic hypertension
- CAD
- Smoking
- BMI
- Height

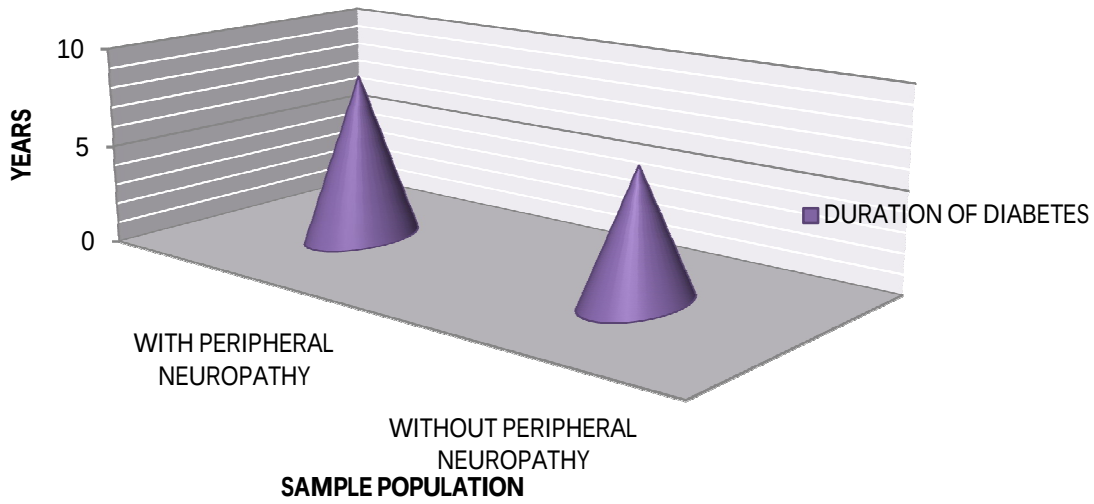
Glycemic control was classified according to HbA1c (%), fasting and postprandial blood sugar values.HbA1c values were measured by spectro – photometry. Patients with blood pressure (BP) more than or equal to 140/90 mm Hg were considered hypertensive. Microalbuminuria was measures by latex turbidimetry. Microalbuminuria is defined as excretion rate of albumin between 20 and 200 mgs/L and macroalbuminuria is measured by protein dip stick . Enzymatic colorimetric method was used for measuring serum cholesterol, Triglycerides, HDL , LDL levels.

Data was analysed using SPSS 17 software after matching for age and sex.

OBSERVATION:

DURATION OF DIABETES

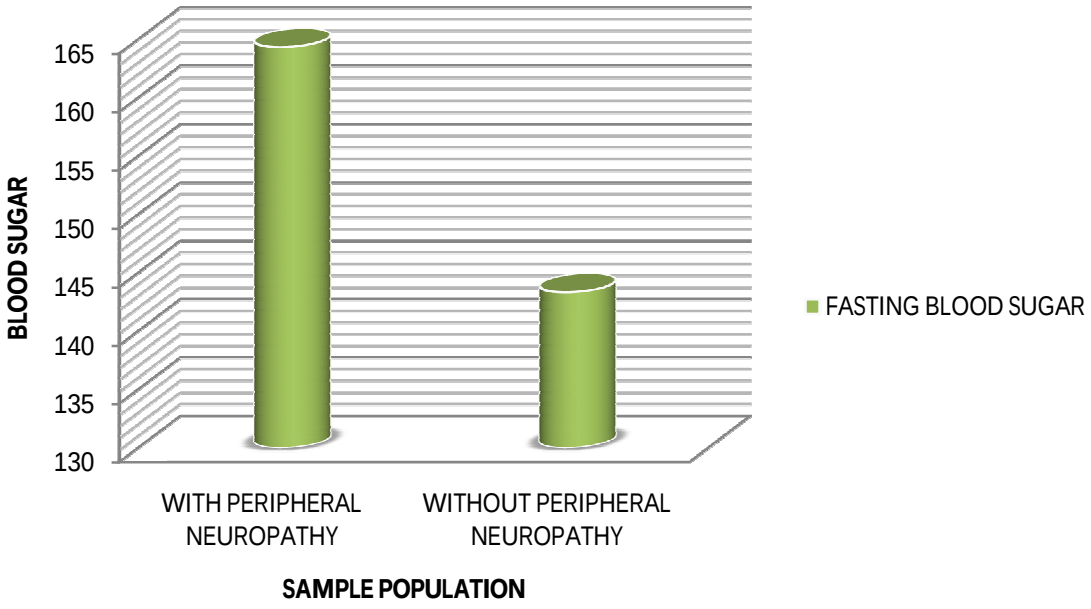
SAMPLE GROUP	MEAN	STANDARD DEVIATION	T - value	p- value
WITH PERIPHERAL NEUROPATHY	8.38	4.54	1.984	0.046
WITHOUT PERIPHERAL NEUROPATHY	6.44	4.71		



The mean duration of treatment for diabetes mellitus in patients with peripheral neuropathy is 8.38 years whereas; in patients without peripheral neuropathy is 6.44 years.

FASTING BLOOD SUGAR:

SAMPLE GROUP	MEAN	STANDARD DEVIATION	T - value	p- value
WITH PERIPHERAL NEUROPATHY	164.34	52.574	1.984	0.0444
WITHOUT PERIPHERAL NEUROPATHY	143.34	48.304		

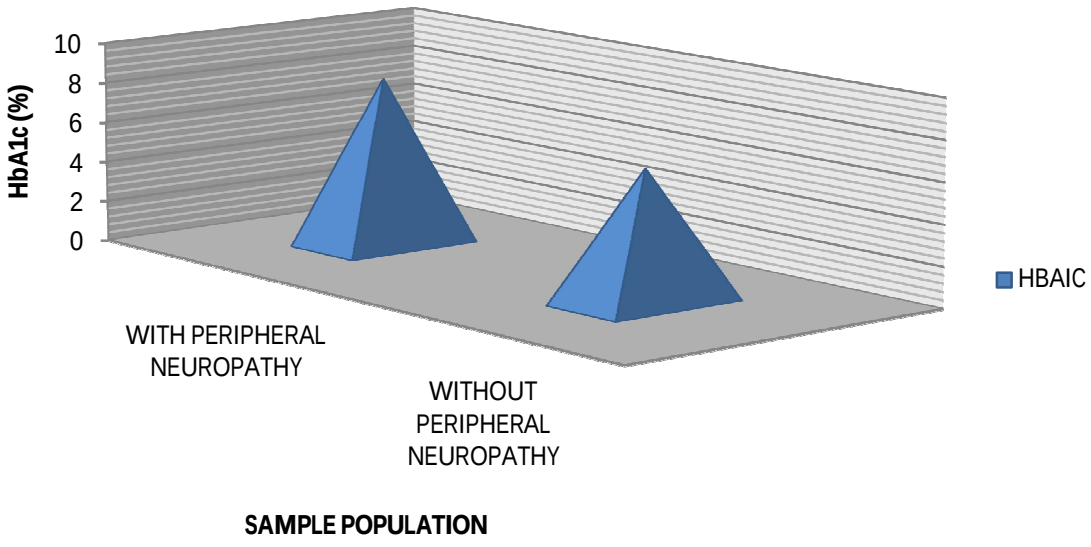


The mean fasting blood sugar value in patients with peripheral neuropathy is 164.34mgs/dl.

In patients without peripheral neuropathy, the mean value is 143.34mgs/dl.

HBAIC:

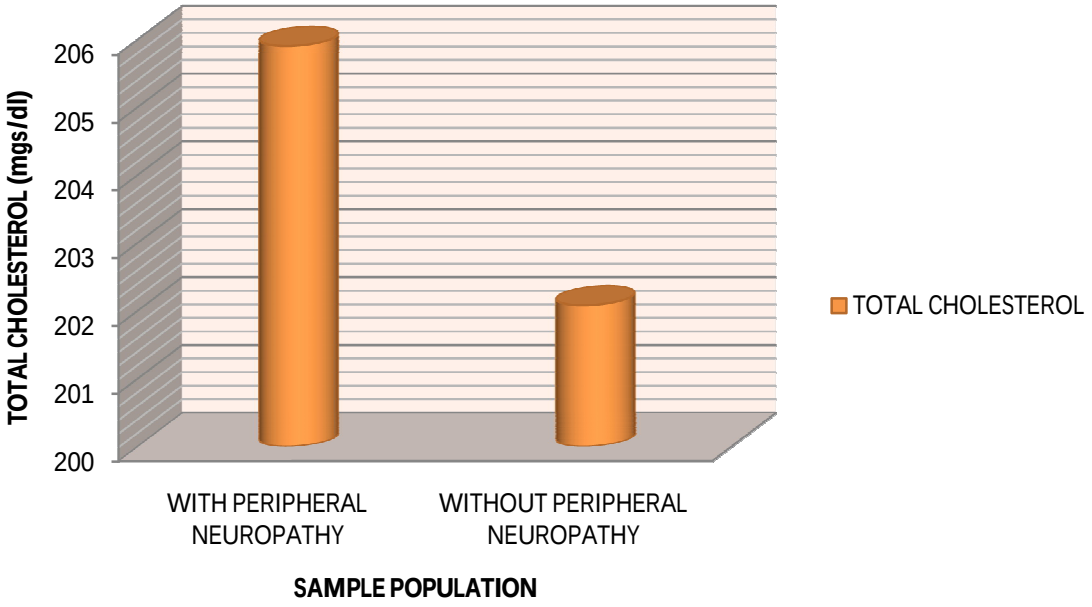
SAMPLE GROUP	MEAN	STANDARD DEVIATION	T - value	p- value
WITH PERIPHERAL NEUROPATHY	9.07	2.61	2.230	0.0280
WITHOUT PERIPHERAL NEUROPATHY	7.92	2.54		



The mean HbA1c value in patients with peripheral neuropathy is 9.07%. In patients without peripheral neuropathy is 7.92%.

TOTAL CHOLESTEROL:

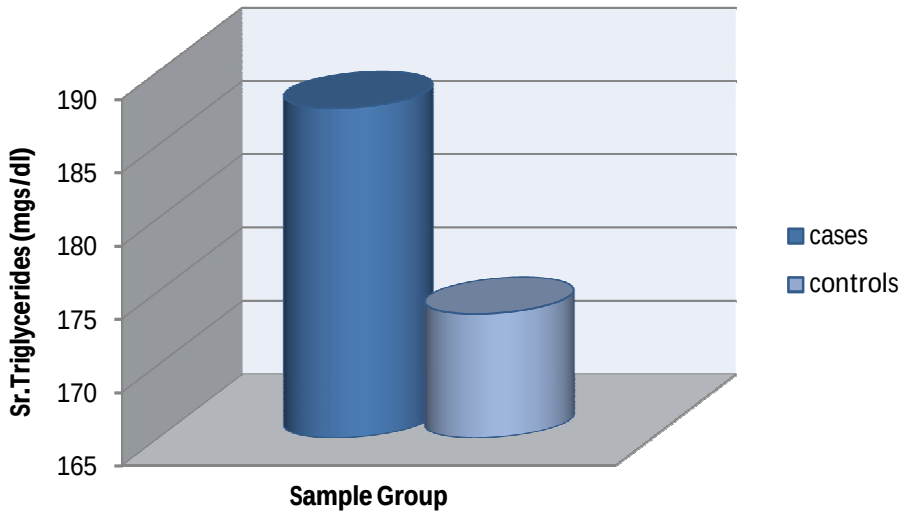
SAMPLE GROUP	MEAN	STANDARD DEVIATION	T - value	p- value
WITH PERIPHERAL NEUROPATHY	205.9	25.879	0.755	0.452
WITHOUT PERIPHERAL NEUROPATHY	202.08	25.508		



The mean Total cholesterol value in patients with peripheral neuropathy is 205.9mgs/dl. In patients without peripheral neuropathy is 202.08mgs/dl. There is no significant difference in patients with and without peripheral neuropathy.

SERUM TRIGLYCERIDES:

SAMPLE GROUP	MEAN	STANDARD DEVIATION	T - value	p- value
WITH PERIPHERAL NEUROPATHY	187.5	29.259	2.6573	0.0092
WITHOUT PERIPHERAL NEUROPATHY	173.46	23.231		



The mean value of triglycerides in patient with peripheral neuropathy is 187.5mgs/dl. The mean value of triglycerides in patients without peripheral neuropathy is 173.46mgs/dl. This difference is statistically significant.

HDL, LDL and VLDL:

HDL:

SAMPLE GROUP	Mean (mgs/dl)	Std. Deviation	T-VALUE	P-VALUE
WITH DPN	56.78	3.489	1.6948	0.0933
WITHOUT DPN	55.549	3.769		

LDL:

SAMPLE GROUP	Mean (mgs/dl)	Std. Deviation	T-VALUE	P-VALUE
WITH DPN	111.62	22.425	0.0617	0.9509
WITHOUT DPN	111.34	22.931		

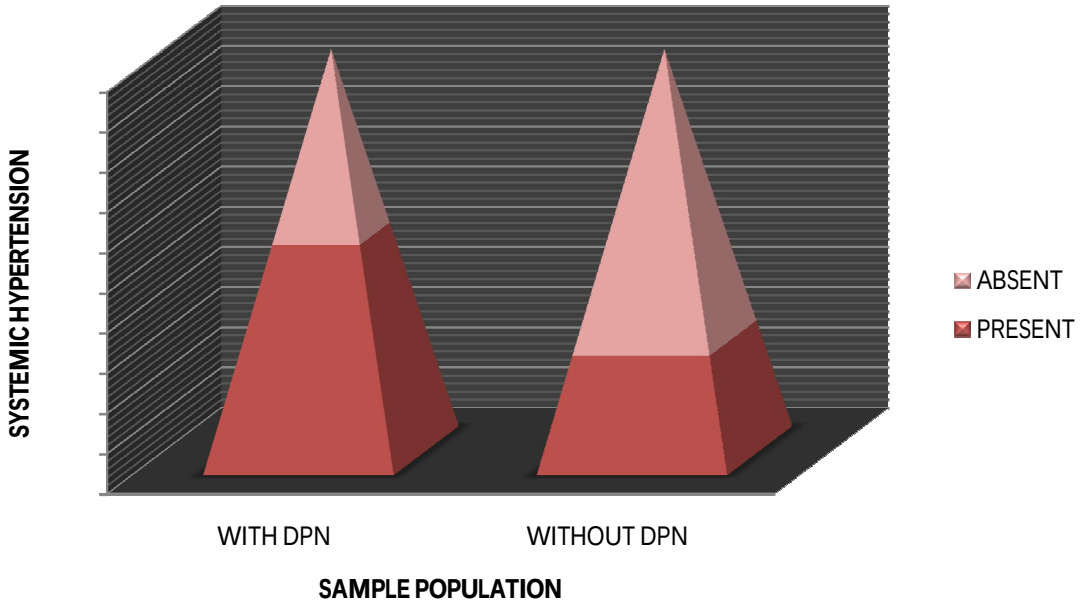
VLDL:

SAMPLE GROUP	Mean (mgs/dl)	Std. Deviation	T-VALUE	P-VALUE
WITH DPN	36.88	5.7627	1.6661	0.0989
WITHOUT DPN	35.18	4.341		

The mean values of HDL, LDL, and VLDL were 56.78mgs/dl,111.62mgs/dl and 36.88mgs/dl respectively in patients with diabetic peripheral neuropathy. In patients without peripheral neuropathy the mean HDL,LDL and VLDL were 55.549 mgs/dl, 111.34mgs/dl, 35.18mgs/dl respectively. The observed differences were not statistically significant.

SYSTEMIC HYPERTENSION:

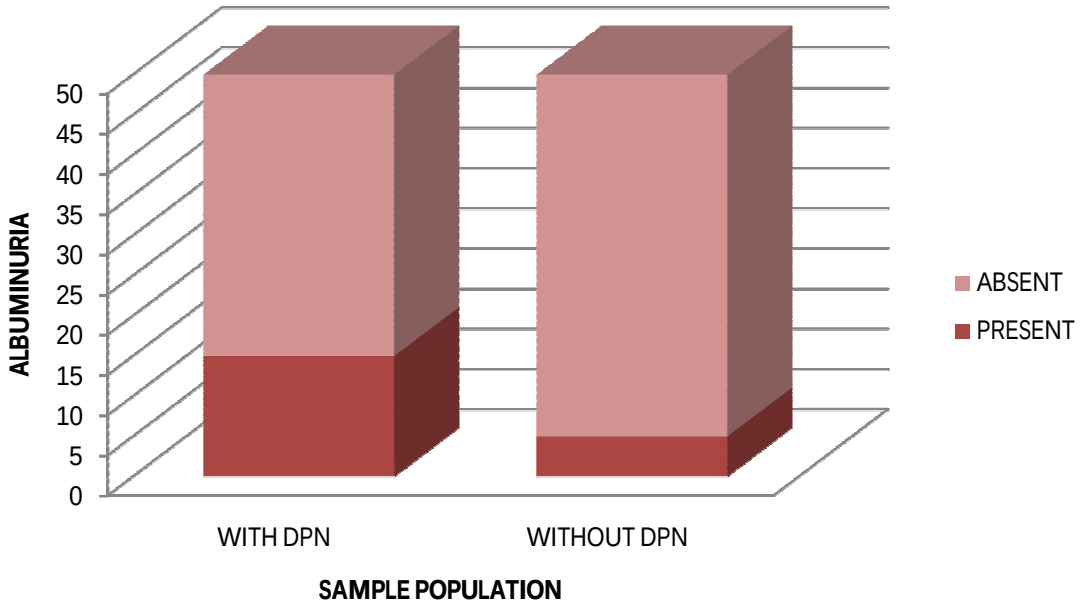
SAMPLE GROUP	STSTEMIC HYPERTENSION		CHI SQUARE TEST P-VALUE
	no	yes	
With Peripheral Neuropathy	23	27	0.0142
Without Peripheral Neuropathy	36	14	



54% of patients with peripheral neuropathy were known hypertensive but among patients without peripheral neuropathy , the prevalence was only 28%.

MACROALBUMINURIA:

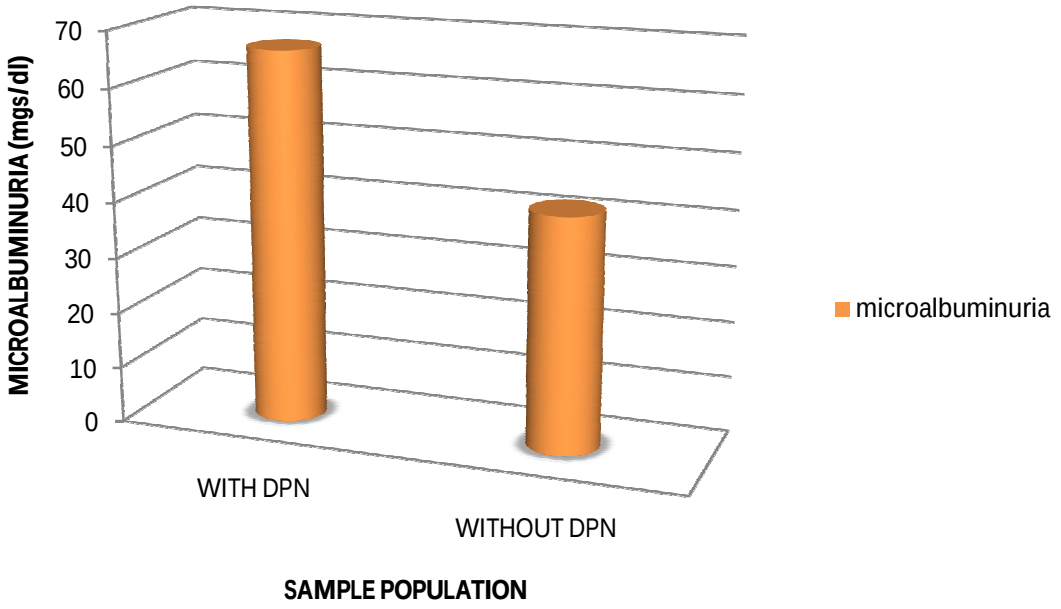
SAMPLE GROUP	ALBUMINURIA		CHI SQUARE TEST P-VALUE
	no	yes	
With Peripheral Neuropathy	35	15	0.0228
Without Peripheral Neuropathy	45	5	



Among patients with peripheral neuropathy, 30% had macroalbuminuria. In patients without peripheral neuropathy only 10% had macroalbuminuria.

MICROALBUMINURIA:

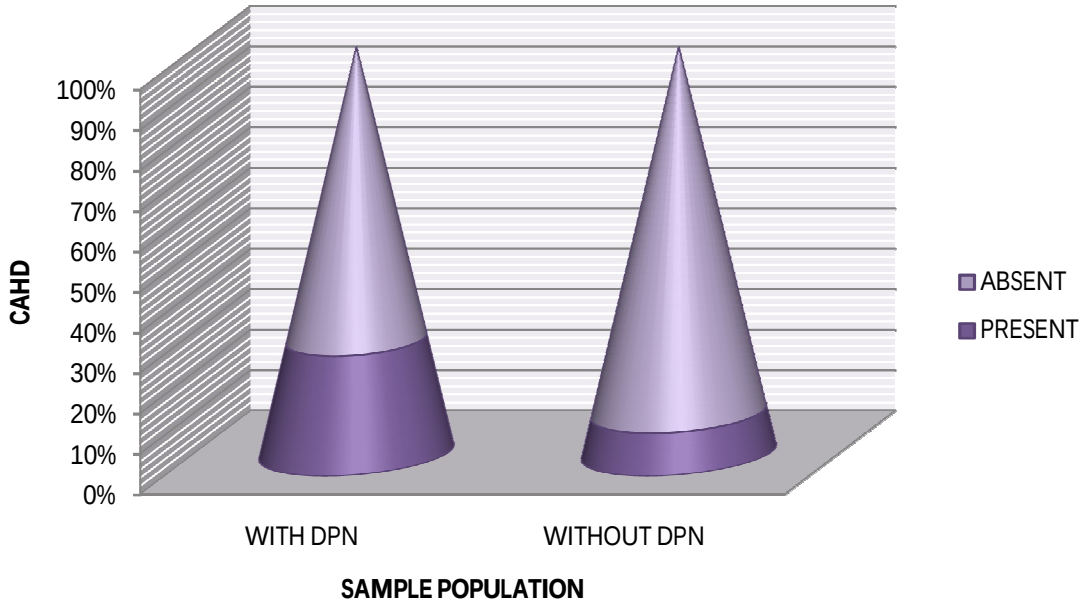
SAMPLE GROUP	N	Mean (mgs/ dl)	Std. Deviation	T- Value	P-Value
WITH DPN	35	66.60	44.504	3.2407	0.0018
WITHOUT DPN	45	41.80	22.660		



The mean microalbuminuria level in patients with diabetic peripheral neuropathy is 66.60 mgs/dl. In patients without diabetic peripheral neuropathy the mean value is 41.80 mgs/dl. This difference is statistically significant.

CORONARY ARTERY HEART DISEASE:

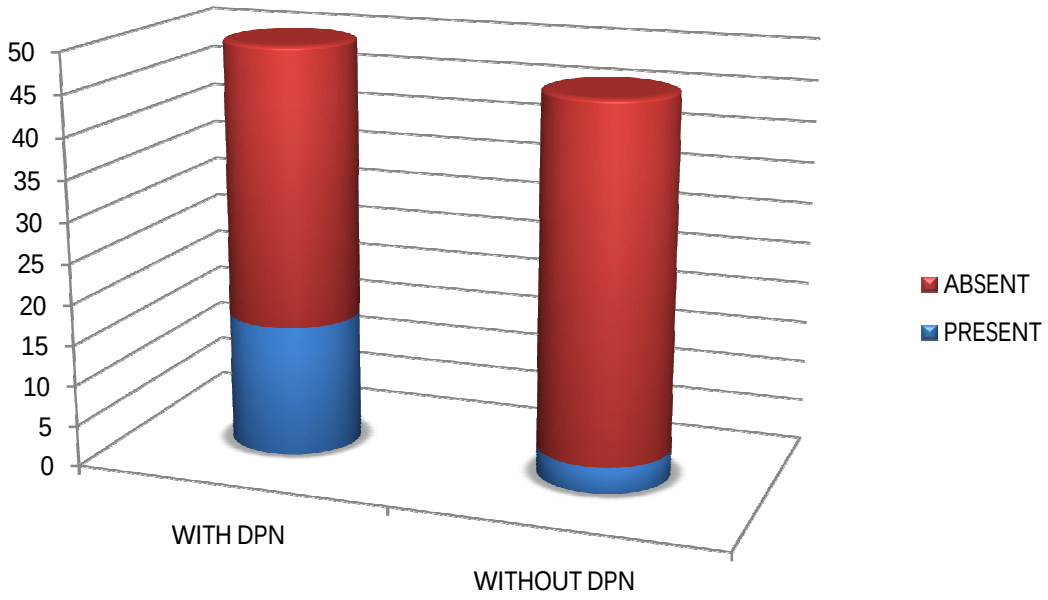
SAMPLE GROUP	CAHD		Chi-square	p-value
	no	yes		
WITH PERIPHERAL NEUROPATHY	36	14	5.263	0.022
WITHOUT PERIPHERAL NEUROPATHY	45	5		



28% of patients with peripheral neuropathy had CAHD. In patients without peripheral neuropathy, only 10% of patients had CAHD.

SMOKING:

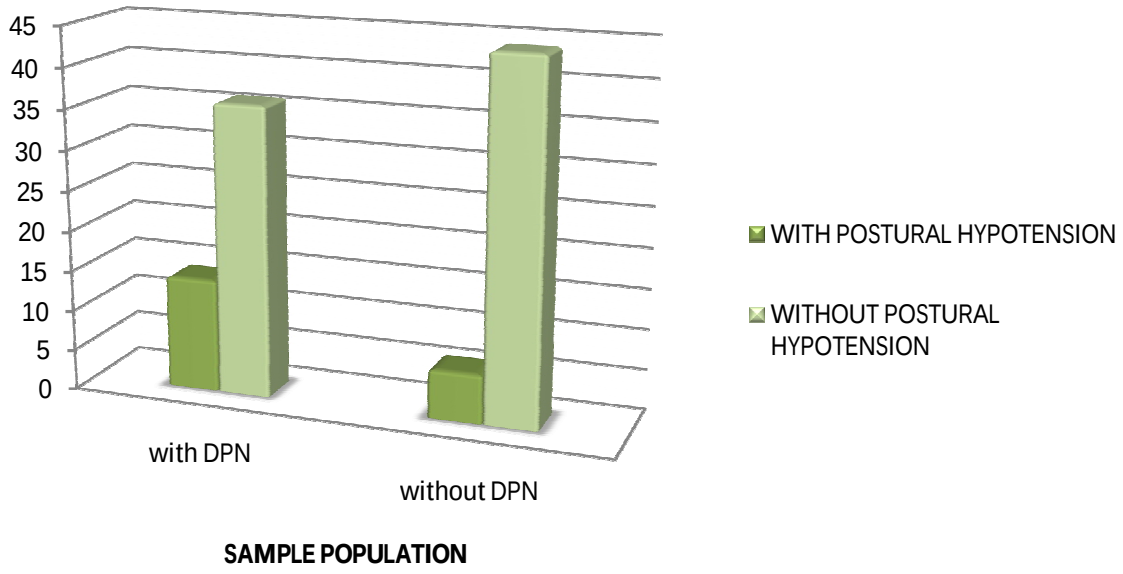
SAMPLE GROUP	SMOKER		Chi-square	p-value
	no	yes		
WITH PERIPHERAL NEUROPATHY	34	16	4.574	0.032
WITHOUT PERIPHERAL NEUROPATHY	43	7		



32% of patients with diabetic peripheral neuropathy were smokers. Among patients without peripheral neuropathy, 14% of patients were non smokers.

POSTURAL HYPOTENSION:

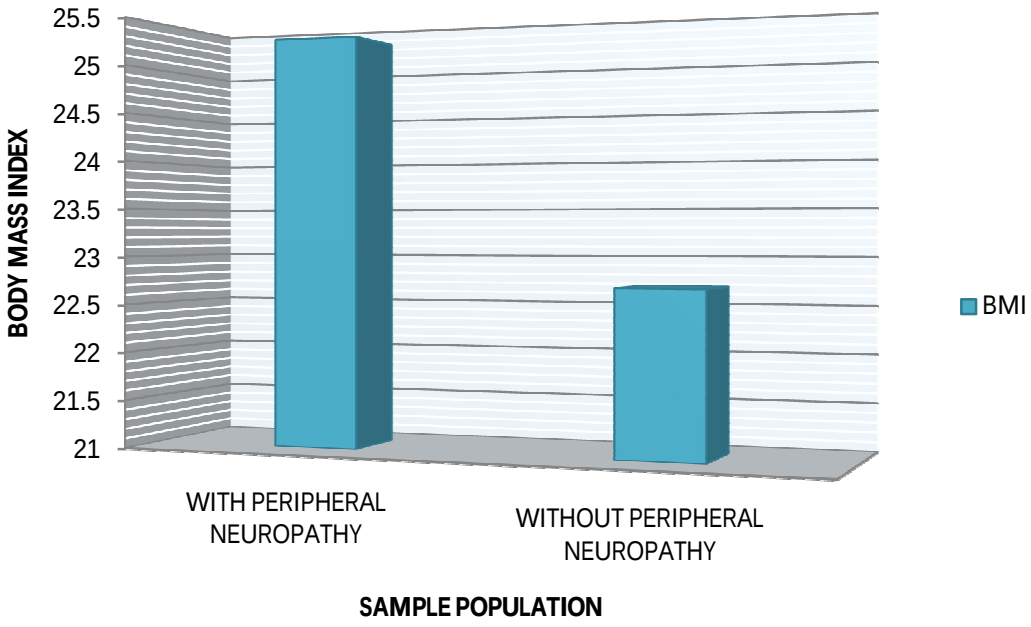
SAMPLE GROUP	POSTURAL HYPOTENSION		p-value
	no	yes	
WITH PERIPHERAL NEUROPATHY	36	14	0.0784
WITHOUT PERIPHERAL NEUROPATHY	44	6	



Among patients with peripheral neuropathy, 28% of them had postural hypotension. Among patients without peripheral neuropathy, only 12% of patients were having a postural fall in blood pressure. However this difference is not statistically significant.

BODY MASS INDEX:

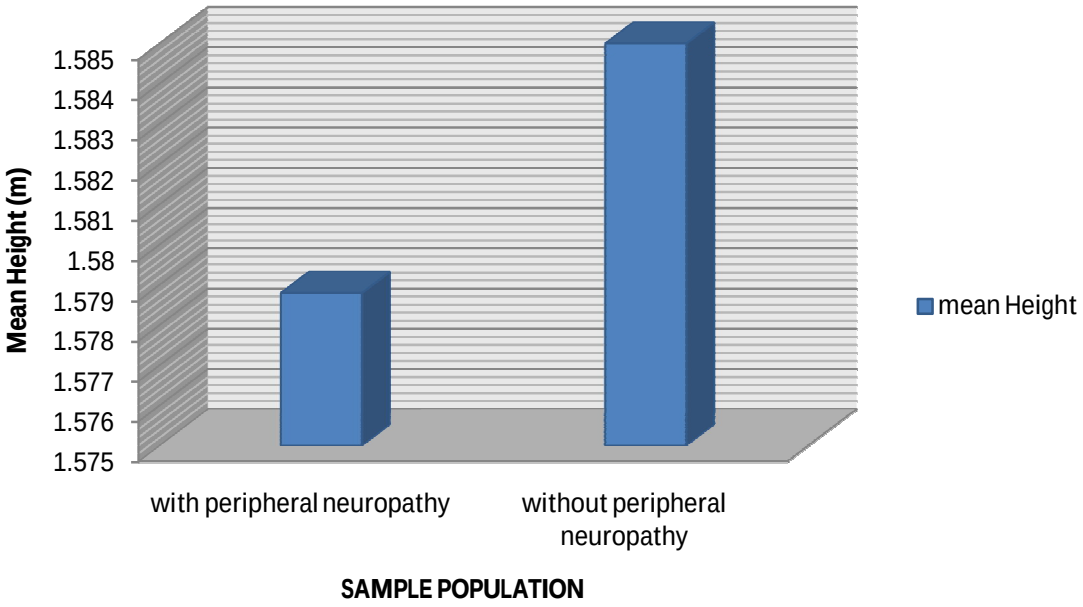
SAMPLE GROUP	Mean	Std. Deviation	T-VALUE	P-VALUE
WITH DPN	25.28	4.025	3.5974	0.0005
WITHOUT DPN	22.7	3.085		



The mean BMI of patients with diabetic neuropathy is 25.28. in patients without diabetic peripheral neuropathy, the mean BMI is 22.7. This difference is statistically significant with a p-value of 0.0005.

HEIGHT:

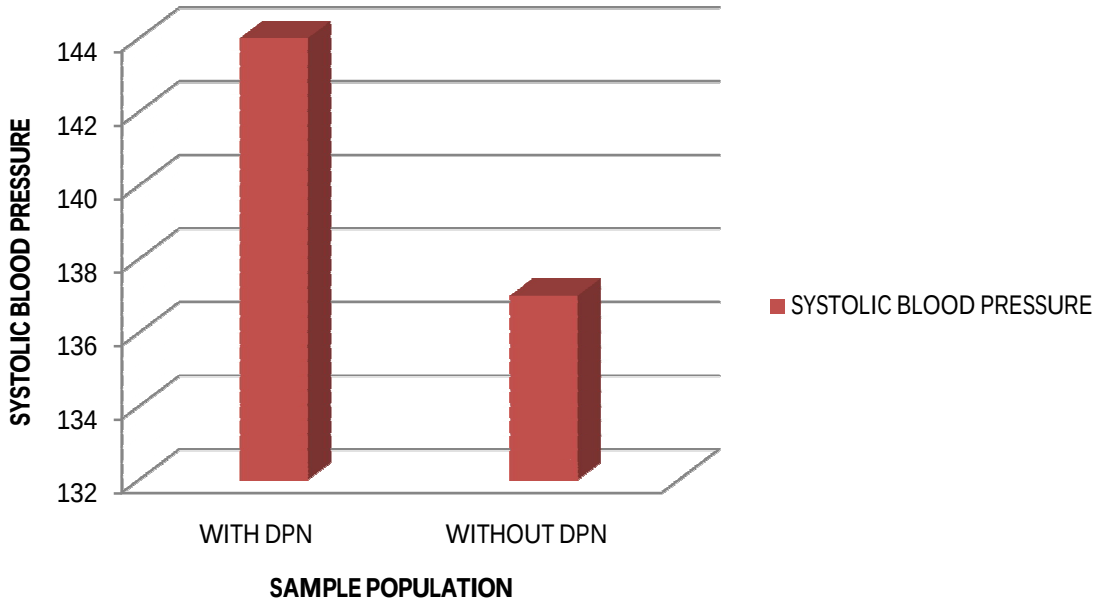
SAMPLE GROUP	Mean (m)	Std. Deviation	T-VALUE	P-VALUE
WITH DPN	1.5788	0.088	0.3282	0.7435
WITHOUT DPN	1.585	0.1005		



In patients without peripheral neuropathy, the mean height was 1.585m. In patients with peripheral neuropathy, the mean height was 1.5788m. This difference is not statistically significant.

SYSTOLIC BLOOD PRESSURE:

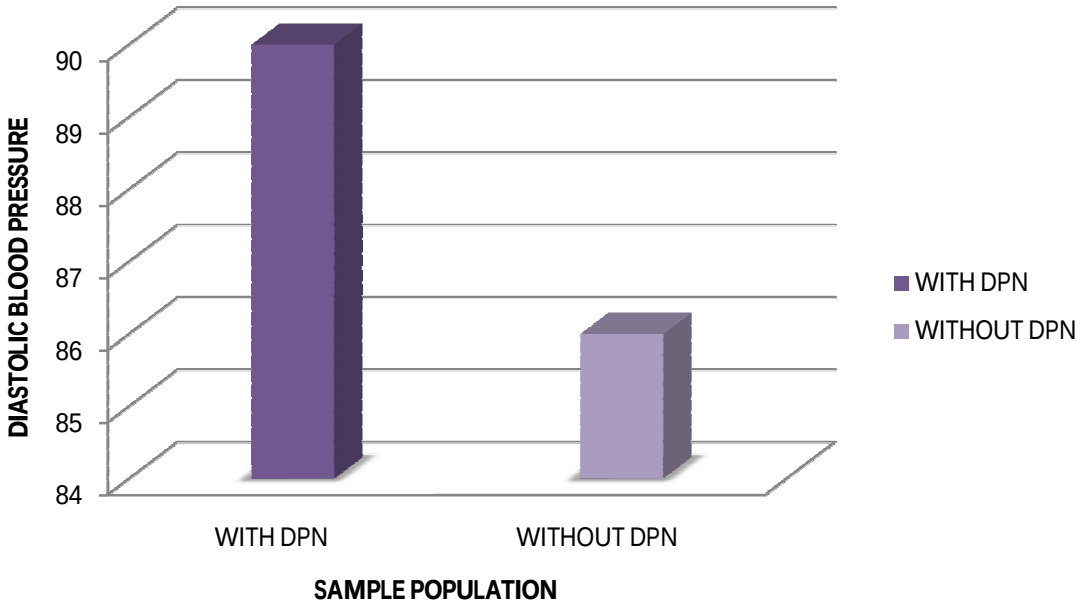
SAMPLE GROUP	Mean (mm hg)	Std. Deviation	T-VALUE	P-VALUE
WITH DPN	144	24	1.6254	o.1073
WITHOUT DPN	138	20		



The mean systolic blood pressure in patients without peripheral neuropathy is 144 mm hg. In patients without peripheral neuropathy the mean systolic blood pressure is 138 mmhg. This difference is not statistically significant.

DIASTOLIC BLOOD PRESSURE:

SAMPLE GROUP	Mean (mm hg)	Std. Deviation	T-VALUE	P-VALUE
WITH DPN	90	15	1.3323	0.1858
WITHOUT DPN	86	13		



The mean diastolic blood pressure in patients with peripheral neuropathy is 90 mmhg. In patients without neuropathy , the mean diastolic blood pressure is 86 mmhg. This difference is not statistically significant.

DISCUSSION:

Diabetic peripheral neuropathy is a common complication of diabetes mellitus with high morbidity and impairment of quality of life. This hospital based, cross-sectional study of risk factors for diabetic peripheral neuropathy conducted in diabetology out patient department, thanjavur medical college hospital during the period of March 2009 to February 2010 found several factors which are significantly associated with an increased risk of peripheral neuropathy which are discussed further.

DURATION OF DIABETES:

This study shows a significant relationship between duration of diabetes and peripheral neuropathy. The mean duration of diabetes mellitus in patients with diabetic neuropathy is 8.38 years in this study.

In Ashok study [125], diabetic peripheral neuropathy showed significant relationship with age, duration of diabetes mellitus. This was a cross-sectional study comprising 1000 consecutive type 2 DM patients attending MV Diabetes speciality centre in South India. In this study mean duration of diabetes in patients with diabetic peripheral neuropathy was 12 years.

This result is in concordance with Tesfaye S et al study [126], J.E.Shaw et al study [127], Booya F et al study [128], Barbosa A P et al study [129], and Ugoya S Oet al study [130].

FASTING BLOOD SUGAR:

This study shows a significant association between fasting blood sugar values and diabetic peripheral neuropathy. Mean FBS values in patients with peripheral neuropathy is 164.34 mg/dl.

Booya Fet al study [128] showed no significant relationship between FBS values and peripheral neuropathy. Similarly, Ashok et al study also showed no significant relationship between the peripheral neuropathy and FBS values. Ugoya S Oet al study [130] showed a significant association between FPG values and peripheral neuropathy. This was a cross-sectional study involving 120 diabetic subjects to determine the risk factors associated with diabetic peripheral neuropathy in Jos University Teaching Hospital, Nigeria.

This result is also in concordance with kumamoto study [131] which concluded that intensive glycemic control would have a beneficial effect on both somatic and autonomic nerve functions.

HbA1c:

High HbA1c levels were associated with peripheral neuropathy. The mean HbA1c level in the present study is 9.07%.

According to UKPDS [132], each 1% reduction in HbA1c levels was associated with a 37% decrease in risk of microvascular complications. EDIC study [133] concluded that the incident and prevalent neuropathy at EDIC 13 to 14 years were influenced by mean A1c levels confirming that poor glycemic control is a significant and robust predictor of neuropathy.

According to Bin lu et al study [134] , which was a cross-sectional risk factor study involving 435 diabetic patients in Shanghai town to evaluate the prevalence of diabetic complications. The mean HbA1c value in patients with diabetic peripheral neuropathy was 7.33%. The study concluded that HbA1c was a significant risk determinant for diabetic peripheral neuropathy.

The diabetes control and complications trial (DCCT) [135] , has established that lowering of HbA1c in patients with IDDM was associated with a reduction in subsequent development of clinical neuropathy.

According to Kumamoto study [131] , the glycemic threshold to prevent the onset and progression of diabetic microvascular complications are as follows, HbA1c < 6.5%, FBS < 110 mgs/dl and 2hr post prandial blood glucose concentration < 180 mgs/dl. Ashok et al study [118] did not show any significant association of HbA1c levels with peripheral neuropathy.

TOTAL CHOLESTEROL:

The study did not show a significant relationship of total cholesterol with diabetic peripheral neuropathy. The mean cholesterol level in patients with diabetic peripheral neuropathy is 205.9mgs/dl. Tesfaye S et al study [126] involved 1172 patients with type 1 DM from 31 centres participating in the EURODIAB diabetes prospective complications study and were studied for risk factors in the development of distal symmetric polyneuropathy. According to this study, there was a significant association of total cholesterol level with the occurrence of peripheral neuropathy. Janghorbani M et al study [137] was a cross-sectional risk factor study for diabetic peripheral neuropathy involving 810 type 2 DM patients. The study did not reveal any significant association of total cholesterol levels with diabetic peripheral nephropathy. Similarly.Ugoya S O et al study[130] did not reveal any significant association of

total cholesterol level with peripheral neuropathy. Ashok et al study [125] also did not show any significant relationship between total cholesterol and peripheral neuropathy.

SERUM TRIGLYCERIDES:

The study revealed significant association of mean serum triglyceride levels with peripheral neuropathy. The mean serum triglyceride level in the study is 187.5mgs/dl. Tesfaye S et al study [136] showed a significant relationship of serum triglyceride levels with peripheral neuropathy. Ashok et al study [125] also reveals significant relation between serum triglyceride level and diabetic peripheral neuropathy.In Wiggin T D et al study [138] data obtained from two identical double blind placebo controlled ,multicentric,52-week clinical diabetic neuropathy trials were analysed. In this cohort of participants with mild to moderate diabetic neuropathy, elevated triglycerides correlated with MFD loss independent of disease duration, diabetes control, or other variables. This hypothesis may explain the earlier incidence of diabetic neuropathy in individuals with type 2 diabetes mellitus compared with individuals with type 1 diabetes mellitus. Dyslipidemia develops later in course of type 1 diabetes and the delayed development of an abnormal lipid profile coincides with delayed onset and progression of diabetic neuropathy[139,140] The correlation between triglycerides and diabetic neuropathy progression suggests that hyperglycaemia and aberrant glucose metabolism are not the only factors contributing to nerve damage. Triglycerides are components of HDL, LDL, and VLDL lipid transporters. When measured in serum, free triglycerides are a surrogate marker of endogenous lipid transport pathway activity. Correction of dyslipidemia with statins has an ameliorative effect on the development and progression of diabetic neuropathy [134,135] .

HDL, LDL AND VLDL:

The study did not reveal an association between HDL, LDL and VLDL levels and peripheral neuropathy. Tesfaye S et al study [136] showed a reduced level of HDL levels in patients with peripheral neuropathy. Schwann cell lipid metabolism has been found to be abnormal.

Maser RE, Steenkiste AR, Dorman JS et al study[143] has also reported a significant association of diabetic peripheral neuropathy with lower HDL cholesterol levels. This may reflect a blood marker of the pathological changes in the myelin structure of nerve.

Ashok et al study[125] does not show any significant association between HDL and diabetic peripheral neuropathy. Elliot J et al study[144] does not show a statistically significant association of HDL levels with the incidence of abnormal VPT after adjustment for A1c and duration of diabetes.

Our result is in concordance with Ugoya S O et al study [130] . The result is also in concordance with Jonghorbani M et al study [137] , which was a cross sectional risk factor study from Isfahm endocrinology and metabolism research centre outpatient clinics, Iran. In this study, 810 patients with type 2 diabetes mellitus were examined. Part of examination included an assessment of neurological function including neuropathic symptoms, physical signs and nerve conduction velocity.

In Tesfaye S et al study[136] ,LDL cholesterol levels showed a significant association in patients with diabetic peripheral neuropathy. According to Elliot J et al study [144] , LDL cholesterol levels showed a significant relationship with the incidence of abnormal VPT after adjustment for HbA1c and duration of diabetes. The Fremantle diabetes study [145] stated that therapy with a statin or a fibrate may protect against the development of diabetic peripheral

neuropathy but there is need for additional confirmatory evidence, preferably randomised clinical trials.

SYSTEMIC HYPERTENSION:

Prevalence of systemic hypertension in patients with peripheral neuropathy is 54%. The association between systemic hypertension and diabetic peripheral neuropathy is statistically different.

The result is in concordance with Tesfaye S et al study [136] . Elliott J et al study[144] showed a significant relationship between systemic hypertension and diabetic peripheral neuropathy. According to UKPDS[146] , the surrogate indices of neuropathy and autonomic neuropathy were not significantly different between patients with and without diabetic peripheral neuropathy.

Booya F et al study[128] did not show any significant association between systemic hypertension and peripheral neuropathy. MaserRE, Steenkisk AR, Dorman JS et al study [143] has reported a significant association between systemic hypertension and diabetic peripheral neuropathy.

Harris M,R ,C.Cowie et al study[147] shows hypertension predisposes to symptoms of sensory neuropathy.

SYSTOLIC BLOOD PRESSURE:

The mean systolic blood pressure in patients with diabetic peripheral neuropathy is 144mmhg. There is no significant difference between mean systolic blood pressure in patients with and without peripheral neuropathy in this study.

Ugoya S O et al study [130] showed a significant relationship between systolic blood pressure and diabetic peripheral neuropathy. Janghorbani M et al study [137] showed a significant association between systolic blood pressure and diabetic peripheral neuropathy.

Cohen J A et al study [148] study was under taken to identify risk factors for the development of diabetic sensory peripheral neuropathy and diabetic autonomic neuropathy, along with their relationship to other diabetic complications, in a representative diabetic population.

The Appropriate Blood pressure Control in Diabetes [ABCD] Trial [149] is comprised of 949 NIDDM patients. A wide range of diabetic sensory peripheral neuropathy risk factors and diabetic complications have been investigated. In this trial systolic blood pressure was significantly associated with diabetic peripheral neuropathy. Ashok et al study [125] showed a significant association between systolic blood pressure and diabetic peripheral neuropathy.

DIASTOLIC BLOOD PRESSURE:

In this study, diastolic blood pressure did not reveal any significant association with diabetic sensory neuropathy. Ugoya S Oet al [130]study showed a significant relationship between diastolic blood pressure and peripheral neuropathy.

Cohen JA et al study [148] did not show a significant association between diastolic blood pressure and diabetic peripheral neuropathy. Janghorbani M et al study [137] did not show a significant association prevalence of peripheral neuropathy and diastolic blood pressure.

S Tesfaye S et al study [136] shows significant trends of increasing prevalence of diabetic peripheral neuropathy with increasing diastolic blood pressure. Ashok et al study[125] did not show a significant association between diastolic blood pressure and peripheral neuropathy

MICROALBUMINURIA:

The study shows significant association between microalbuminuria and the prevalence of peripheral neuropathy. The mean microalbuminuria value in peripheral neuropathy patients is found to be 66.6mgs/dl.

In Lluch et al study [150] , which was a cross-sectional study involving 100 type 1 DM patients. Patients were studied for risk factors contributing to peripheral neuropathy and autonomic neuropathy. In Tesfaye S et al study[136] , the presence of microalbuminuria was a significant predictor of peripheral neuropathy. Elliott J et al study [144] showed a significant association between the incidence of abnormal VPT and after adjustment for A1c and duration of diabetes and microalbuminuria.

S.Savage et al study[151] was a large population was a large population study of 947 NIDDM patients living predominantly in a metropolitan area. This study shows that urine albumin excretion is significantly associated with neuropathy. This suggests that UAE may be more than an indicator of renal disease in NIDDM patients and in fact, may reflect a state of generalised vascular damage occurring throughout the body.

MACROALBUMINURIA:

In this study 30% of patients with DPN had macroalbuminuria. The study shows a significant association between macroalbuminuria and DPN. Elliott J et al study[144] shows a significant association between the incidence of abnormal VPT and macroalbuminuria after adjustment for A1c and duration of diabetes.

Solomon Tesfaye S et al study [136] shows significant association between newly diagnosed neuropathy and macroalbuminuria with an odds ratio of 1.48. In EURODIAB IDDM complications study[126] , multiple logistic regression analysis of DPN shows macroalbuminuria as a significant risk factor.

Coppini D V et al study[152] study did not show a significant association between prevalence of DPN and macroalbuminuria. J.E.Shaw et al study [127] showed a significant association between macroalbuminuria and DPN.

Bin Lu et al study[134] showed that the percentage of macroalbuminuria in DPN group (9.0%) was significantly higher than that in the non – DPN group (1.8%). J.E.Shaw et al study[127] found that a significant number of patients with diabetic nephropathy did not have peripheral neuropathy.

SMOKING:

This study shows smoking has a significant association with peripheral neuropathy. In Mitchell B D et al study[153] , it is shown that the risk for neuropathy was 3 times higher in smoking type 1 DM patients than in non-smokers. Smoking was not related to neuropathy in type 2 DM patients.

Christen WG et al study[154] in young IDDM patients, it was shown that apart from glycemic control, cigarette smoking may be an independent risk factor for progression of distal sensory neuropathy. In Masser RE et al [143] and Reichard P et al studies [155] , in type 1DM patients have confirmed the roles of glycemic control as well as smoking habits for the development of clinical neuropathy.

In Maser RE et al study[143] smoking status was found to be significantly associated with neuropathy in the models for > or = 18 yr old group and > or = 30 year old group. In Mitchell B Det al study [146] , cigarette smoking was significantly associated with DPN. According to Harris M et al study[147], height was not a significant risk determinant of peripheral neuropathy.

According to A.I.Alder et al study [156] , neuropathy was less common in current smokers than subjects not currently smoking. In Janghorbani M et al study [137] smoking was not related to prevalence of sensory neuropathy. According to Tesfaye S et al study [136] cigarette smoking has been associated with peripheral neuropathy. K.Kasim et al study[157] was a cross-sectional study conducted in Al-Azhar University hospitals, Cairo, Egypt, recruited 300 patients with type 2 DM patients who are attending diabetic clinics in the studied hospital from Oct 2005 through Jan 2006, showed no significant association between smoking and peripheral neuropathy. Elliott J et al study [144] shows significant association between and DPN. In EURODIAB IDDM complications study [126] , smoking was significantly associated with the prevalence of DPN.

CORONARY ARTERY HEART DISEASE:

The study showed a significant association between the history of CAHD and prevalence of DPN. In Ashok et al study[125] showed a good correlation between history of CAHD and prevalence of DPN.

In EURODIAB IDDM complications study[126] , significant association was found between the prevalence of DPN and the presence of cardiovascular disease. Owlabi MO et al study [158] shows aggregate cardiovascular load was a stronger statistical correlate and predictor of clinically evident DPN.

According to Barbosa A P et al study [129], CAHD is significantly associated with DPN. Elliott J et al study [137] the presence of cardiovascular disease at baseline seem to predict the development of abnormal VPT. In Davis T M E et al study[145], the presence of CVD at baseline is associated with the prevalence of DPN. In Janghorbani M et al study [137], significant number of patients with peripheral neuropathy had CAHD. According to Tesfaye S et al study [136] the incidence of neuropathy is associated with CAHD.

BMI:

The study shows statistically significant association between obesity and DPN. According to Coppini D V et al study [152] , higher BMI was associated with prevalence of DPN. In K.Kasim et al study [157] risk was reduced among married and obese patients. In Bruce SGet al study [159] increased BMI levels are significantly associated with the prevalence of DPN.

In Janghorbani M et al study[137] , BMI levels are not significantly associated with DPN. According to Ugoya S Oet al study[130], BMI levels are not significantly associated with DPN.

In Tesfaye S et al study[136], after adjustment of HbA1c and duration of diabetes, found that higher levels of BMI were significantly associated with the cumulative incidence of neuropathy.

In Bin Lu et al study[134], the DPN patients were older and had higher BMI when compared with patients without neuropathy.

HEIGHT:

In this study there was no significant association between patients with and without peripheral neuropathy. The mean height of patients with peripheral neuropathy is 1.57 metres. J.E.Shaw et al study [127],shows a significant association between height and DPN. M.T.Gadia et al study[160] shows significant relationship between height and DPN. Tesfaye S et al study [136] showed significant trends of increasing prevalence of diabetic peripheral neuropathywere only observed with increasing height. Elliott J et al study[144] ,shows association between the incidence of abnormal VPT and height after adjustment for HbAic and duration of diabetes. Alder AI et al study [156] shows significant difference in height between patients with and without peripheral neuropathy. Janghorbani M et al study [137] didnot show significant association between height and DPN. Tesfaye S et al study [136] did not show any significant association between height and DPN.

Davis T M E et al study [142] did not show any significant association between height and DPN. Sosenko JM et al study[161] showed significant increased incidence of DPN in taller patients.

Lawrence .R .Robinson et al study [162]supports the hypothesis that height is an important risk factor for polyneuropathy in diabetic subjects.

POSTURAL HYPOTENSION:

Postural hypotension was measured to assess the integrity of autonomic nercous system. This study shows a significant association between postural hypotension and DPN.

Ugoya S Oet al study [130] shows a significant association between autonomic neuropathy and DPN. Elliott J et al study[144] shows a significant association between cardiac autonomic neuropathy and DPN.

Lluch I et al study [150] was a cross-sectional study involving 100 type 1 DM patients. This study concluded that cardiovascular autonomic neuropathy is frequent in type 1 DM patients, furthermore, prevalence increases with existence of peripheral neuropathy and duration of diabetes.

SUMMARY:

1. One hundred patients with type 2 diabetes were included in the study.
2. Patients were randomised to two groups of 50 each. Group 1 included patients without neuropathy and group 2 included patients with neuropathy.
3. The two groups were matched for age and sex.
4. The mean duration of treatment for diabetes mellitus in group 2 patients is 8.38 years which is statistically significant.
5. The mean fasting blood sugar value in group 2 patients is 164.34mgs/dl which is statistically significant.
6. The mean HbA1c value in group 2 patients is 9.07% which is statistically significant.
7. The mean Total cholesterol value in group 2patients is 205.9mgs/dl whereas the mean value in group 1 patients is 202.08mgs/dl.
8. The mean value of triglycerides in group 2 patients is 187.5mgs/dl which is statistically significant.
9. The mean values of HDL, LDL, and VLDL were 56.78mgs/dl,111.62mgs/dl and 36.88mgs/dl respectively in group 2 patients. In group 1 patients the mean HDL, LDL and VLDL were 55.549 mgs/dl, 111.34mgs/dl, 35.18mgs/dl respectively.
10. 54% of patients in group 2 had systemic hypertension whereas in group 1 it was 28%. This difference is statistically significant.
11. The mean systolic blood pressure in group 1 patients is 138 mm of hg whereas in group 2 patients it is 144 mm of hg.
12. The mean diastolic blood pressure in group 1 patients is 86 mm of hg whereas in group 2 patients it is 90 mm of hg.
13. 30% of patients in group 2 had macroalbuminuria which is statistically significant.

14. The mean microalbuminuria level in group 2 patients is 66.60mgs/dl which is statistically significant.
15. The mean BMI in group 2 patients is 25.28. It is statistically significant.
16. In group 1patients, the mean height is 1.5788m. In group 2 patients, the mean height is 1.585m.
17. 28% of patients in group 2 had history of CAHD and this is statistically significant.
18. 32% of patients in group 2 were smokers. This is statistically significant.
19. 12% of patients in group 1 had postural hypotension whereas in group 2 28% of the patients were having postural hypotension.

CONCLUSION:

Among the risk factors hyperglycemia is the modifiable risk factor for diabetic neuropathy, intensive glycemic control is the established therapy for reducing the incidence or slowing the progression of neuropathy. Other contributory factors include duration of diabetes, fasting blood sugar, HbA1c, serum Triglycerides, macroalbuminuria, microalbuminuria, Systemic hypertension, history of smoking, coronary artery heart disease, BMI. Improved preventive care and earlier intervention may improve the disease outcome, prevent or delay the onset of neuropathy and consequently have a positive impact on patients quality of life and reduce the economic burden of diabetes and its complications.

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PROFORMA

Name: Age: Sex:

Occupation: Address: OP/IP NO:

History:

1. Age at the diagnosis of diabetes
2. Duration of treatment for diabetes
3. H/O Smoking
4. H/O Hypertension; CAHD ; Stroke

Neuropathic symptoms:

H/o numbness or coldness of feet

H/o pricking sensation in feet

H/o deep or burning sensation in feet

H/o unusual difficulty in climbing stairs

H/o dizziness on standing

H/o chronic diarroea (at night)

H/o Gustatory sweating

H/o Erectile dysfunction

TREATMENT HISTORY:

ANHROPOMETRY:

Height: Weight: BMI:

Waist Circumference: Hip circumference:

Waist/ Hip ratio :

Blood pressure: Supine: Standing:

INVESTIGATIONS:

HbA1c:

Fasting Blood sugar:

Post prandial Blood Sugar:

Urea:

Creatinine:

HB%:

Lipid profile:

HDL TGL LDL VLDL

Albuminuria:

Microalbuminuria:

ECG IN ALL LEADS:

MASTER CHART

S.NO	GROUP	ROLL.NO	OP.NO	NAME	AGE	SEX	DURATION OF TREATMENT	HBA1C	FBS	PPBS	T.CHOLESTEROL	TGL	HDL	LDL	VLDL	ALBUMIN	MICROALBUMINURIA	SBP	DBP	HEIGHT	WEIGHT	BMI	SHT	CAHD	POSTURAL HYPOTENSION	SMOKER
1	2	1	1457/06	vasudevan	74	M	4	8.7	130	270	189	206	53	95	41	nil	139	136	84	1.7	80	27	no	yes	yes	no
2	2	2	956/03	samiaiya	64	M	27	14.1	170	326	178	184	55	87	36	yes		171	88	1.58	52	20	yes	no	no	yes
3	2	4	1095201	sabiakani	50	F	22	12.7	282	422	261	214	57	161	39	nil	42	130	76	1.56	48	19	no	yes	no	no
4	2	5	1094400	sabiabeevi	60	F	5	6.2	320	388	217	219	61	112	44	yes		129	82	1.57	65	26	no	no	no	no
5	2	6	1095393	Thamanan	41	M	5	15.7	201	382	214	167	53	128	33	nil	157	114	82	1.64	75	27	no	no	no	no
6	2	7	1461/05	chandra	47	F	7	12.9	167	243	221	162	59	130	32	yes		131	105	1.55	68	28	yes	yes	yes	no
7	2	8	1340/10	palaniammal	50	F	4	7.9	271	364	241	218	57	140	33	nil	54	179	96	1.52	60	25	yes	no	yes	no
8	2	9	156/03	govindaraj	75	M	15	8.9	170	270	188	167	54	101	33	yes		122	66	1.51	65	28	yes	yes	no	yes
9	2	10	159/07	krishnammal	60	F	7	11.8	179	256	201	179	58	107	36	nil	104	180	100	1.41	62	31	yes	no	yes	no
10	2	11	340/07	pattu	70	F	5	7.2	130	206	195	172	61	100	34	nil	36	190	100	1.44	60	28	yes	no	no	no
11	2	12	430/06	rajalakshmi	50	F	10	12.4	200	298	207	169	58	115	34	nil	149	176	111	1.42	57	28	yes	yes	yes	no
12	2	13	1017/05	saroja	60	F	5	6.3	131	229	189	162	51	106	32	nil	44	156	108	1.5	75	33	yes	no	no	no
13	2	14	3410/03	valli	49	F	9	13.7	200	310	186	164	57	96	33	nil	62	120	85	1.48	64	29	no	no	no	no
14	2	15	1104/08	geetha	52	F	10	10.8	190	326	209	167	61	115	33	nil	77	158	93	1.53	70	29	no	no	yes	no
15	2	16	109626	leelavathy	62	F	7	6.1	160	217	214	183	59	118	37	nil	119	188	115	1.49	62	27	yes	no	no	no
16	2	17	1243/03	susaimary	65	F	10	8.9	153	266	184	149	56	98	30	nil	67	144	78	1.41	49	24	no	no	no	no
17	2	18	437/0	muthuku	38	M	6	13.7	137	304	226	147	51	146	29	nil	187	114	84	1.67	67	24	no	no	no	no

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			6	mar																					
18	2	19	138/04	kamachi	77	M	7	7.9	156	238	221	198	59	122	37	yes		131	62	1.72	60	20	no	no	no	no
19	2	20	431/07	saroja	58	F	7	8.1	120	218	204	193	59	106	39	nil	37		95	1.49	70	31	yes	no	no	no
20	2	21	1373/07	padma	40	F	14	12.7	225	406	176	219	58	75	34	yes		151 148	80	1.46	70	32	no	no	yes	no
21	2	25	1097423	mariappan	64	M	6	8.8	123	212	187	172	61	89	37	nil	29	100	60	1.68	65	23	no	no	no	no
22	2	26	346/07	ayyamperumal	77	M	7	9.1	237	388	192	173	58	99	35	yes		113	72	1.69	45	15	no	no	no	no
23	2	27	1099595	ramachandran	64	M	14	11.2	145	198	183	207	56	86	41	yes		141	71	1.59	56	22	yes	yes	yes	yes
24	2	28	1097371	nagammal	57	F	5	8.4	104	247	231	217	62	126	43	nil	147	110	70	1.41	61	30	no	no	no	no
25	2	29	411/07	shanmugam	66	M	10	7.9	132	212	248	207	62	145	41	nil	58	150	90	1.7	76	26	yes	yes	yes	yes
26	2	30	1307/06	jeyakumar	51	M	12	8.7	211	289	198	176	55	108	35	nil	62	210	104	1.65	62	22	yes	yes	yes	no
27	2	31	341/06	selvaraj	62	M	10	7.2	113	189	249	218	62	143	44	yes		191	109	1.58	62	24	yes	no	no	no
28	2	32	374/08	ramaiyan	70	M	7	9.5	188	286	188	167	53	102	33	nil	74	150	90	1.7	70	24	yes	no	no	no
29	2	33	1219/04	murugan	60	M	9	8.8	148	232	193	261	57	83	52	nil	68	138	74	1.64	57	21	no	no	no	no
30	2	34	1315/04	idumbaiyan	54	M	6	8.2	148	284	257	276	63	139	55	yes		127	90	1.62	56	21	no	no	no	yes
31	2	35	114/03	duraimanickam	67	M	12	10.2	200	336	193	217	58	92	43	nil	71	135	92	1.66	57	20	no	no	no	no
32	2	36	1412/07	balasubramaniam	42	M	15	11.2	124	228	188	209	57	89	42	yes		135	92	1.66	57	20	no	no	no	no
33	2	37	411/04	veeraiyan	62	M	11	9.1	228	364	261	197	58	164	39	nil	18	131	89	1.56	62	25	no	yes	no	no
34	2	38	1311/05	sadhasivam	70	M	5	8.6	256	416	219	168	55	130	34	nil	59	132	86	1.52	55	23	yes	yes	no	no
35	2	40	1131/08	manikaraj	70	M	7	6.1	100	178	187	179	56	95	36	nil	31	155	111	1.68	62	21	yes	no	no	yes
36	2	41	239/05	sundaram	80	M	8	7.3	98	134	189	147	52	108	29	nil	16	133	74	1.61	54	20	no	no	no	no

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37	2	42	1323/06	loganathan	56	M	5	6.2	134	228	178	161	53	93	29	nil	29	171	113	1.66	76	27	yes	no	yes	no
38	2	43	233/02	abdul hameed	54	M	6	5.3	112	132	184	179	56	92	36	nil	23	143	93	1.59	62	24	yes	no	no	no
39	2	51	1411/08	sethu	67	M	6	8.6	146	212	187	172	54	99	34	nil	66	122	76	1.62	70	26	no	no	no	no
40	2	52	611/07	devdas	43	M	5	13.1	150	264	207	181	56	115	36	nil	97	127	79	1.49	80	36	yes	no	no	no
41	2	53	2313/08	saarangappan	62	M	11	5.7	100	176	195	174	49	111	35	yes		135	90	1.69	70	24	no	no	no	no
42	2	59	3103/06	paneerselvam	62	M	10	6.3	114	189	191	172	55	102	34	nil	27	150	100	1.5	60	26	yes	no	yes	no
43	2	60	1848/08	santhana	56	M	4	8.1	211	316	187	149	51	106	30	nil	39	130	80	1.6	62	24	no	no	no	yes
44	2	61	411/05	sebastein	67	M	10	6.3	98	134	174	139	51	95	28	nil	25	122	76	1.62	67	25	no	no	no	yes
45	2	72	1621/10	arpudhan	60	M	8	6.4	112	168	207	184	59	111	37	yes		150	100	1.54	64	26	yes	no	no	yes
46	2	73	1313/08	veemarajan	73	M	4	6.6	114	145	208	211	62	104	42	nil	49	140	90	1.68	76	26	yes	yes	yes	no
47	2	75	2083/08	sayed	74	M	4	5.8	136	123	176	161	59	85	32	nil	22	170	102	1.6	77	30	yes	no	no	no
48	2	76	958/07	kaliyamoorthy	66	M	3	8.7	144	211	191	218	53	94	44	nil	47	120	80	1.65	78	28	yes	yes	yes	yes
49	2	81	1679/09	mahendran	51	M	5	11.6	237	404	267	241	58	161	48	yes		172	116	1.55	62	25	yes	yes	no	no
50	2	97	732/02	moorthy	60	M	8	7.8	162	288	259	203	61	157	41	yes		156	118	1.55	60	24	yes	yes	no	no
51	1	3	1330/02	ganesan	53	M	7	8.1	153	228	191	188	57	96	38	nil	85	128	85	1.6	52	20	no	no	no	
52	1	22	311/07	murugana ndhan	43	M	6	8.3	212	289	192	163	51	108	33	yes		142	81	1.61	70	27	no	no	no	no
53	1	23	2131/05	paulraj	60	M	4	8.1	72	116	201	183	56	108	37	nil	42	130	90	1.55	60	24	no	no	yes	
54	1	24	1096396	ganesan	73	M	18	5.9	308	304	197	173	58	102	34	nil	22	134	78	1.55	58	24	no	no	no	no
55	1	39	4151/	rajappa	46	M	5	5.6	285	286	262	173	55	172	35	nil	27	100	70	1.59	57	22	no	no	no	no

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			08																						
56	1	44	175/10	govindasamy	73	M	2	6.7	121	213	228	179	55	137	36	nil	31	147	97	1.51	48	21	no	no	no	yes
57	1	45	550/02	rangarajan	64	M	10	10.8	114	189	187	162	54	101	32	nil	79	129	82	1.74	59	19	no	no	no	no
58	1	46	1171/08	panjanathan	60	M	5	6.1	122	206	193	171	56	103	34	nil	24	145	94	1.56	66	27	yes	no	no	no
59	1	47	789/00	saroja	58	F	4	5.9	112	187	181	161	59	89	33	nil	19	135	72	1.45	56	26	yes	yes	no	no
60	1	48	414/08	rajalakshmi	52	F	6	12.7	118	126	189	157	48	110	31	nil	109	152	88	1.49	46	20	no	no	no	no
61	1	49	1319/09	mahadevi	49	F	5	6.7	168	304	178	149	56	92	30	nil	33	153	114	1.54	50	21	no	no	no	no
62	1	50	615/07	john britto	53	M	5	7.9	105	234	271	213	62	166	43	nil	47	155	110	1.59	64	25	no	no	no	no
63	1	54	1172/05	selvarani	61	F	7	5.5	132	188	204	181	56	112	36	nil	23	138	92	1.4	55	28	no	no	yes	
64	1	55	516/01	ramarasu	58	M	4	6.1	108	168	202	166	54	115	33	nil	24	163	87	1.58	55	22	no	no	no	no
65	1	56	220/09	rasammal	48	F	6	10.8	123	188	209	161	58	111	40	nil	67	159	91	1.54	84	35	no	no	no	no
66	1	57	128/06	ragina mary	61	F	4	11.6	180	224	211	189	62	111	38	nil	49	140	80	1.57	72	29	yes	no	no	no
67	1	58	424/05	lalitha	57	F	17	6.7	223	304	183	162	54	97	32	yes		180	94	1.5	54	24	yes	yes	no	no
68	1	62	753/05	varadarajan	51	M	5	9.2	94	150	212	196	57	116	39	nil	85	120	80	1.65	60	22	no	no	no	no
69	1	63	9101/03	rangammal	60	F	7	6.1	240	256	192	173	56	101	35	nil	24	120	80	1.4	45	22	no	no	no	no
70	1	64	2216/09	rasu	50	M	5	5.7	130	240	196	167	49	114	33	nil	19	120	80	1.67	51	18	no	no	yes	
71	1	65	2104/07	john	40	M	3	5.9	123	268	207	183	56	114	37	nil	31	120	80	1.55	50	20	no	no	no	no
72	1	66	754/10	rajendran	55	M	3	14.1	160	236	219	196	57	123	39	nil	39	130	80	1.62	64	24	no	no	no	yes
73	1	67	3405/05	amsavalli	67	F	4	5.9	168	213	231	186	55	139	37	nil	22	110	70	1.42	42	20	no	no	no	no

MASTER CHART

74	1	68	1856/08	vijayalakshmi	54	F	4	6.1	150	240	169	127	46	98	25	nil	24	120	80	1.43	45	22	no	no	no	no
75	1	69	2334/08	ramalingam	42	M	3	5.7	119	254	197	181	56	105	36	nil	21	130	90	1.85	75	21	no	no	no	no
76	1	70	3004/02	lakshmi	70	F	15	6.1	142	264	187	149	55	102	30	nil	27	130	80	1.46	45	21	no	no	no	no
77	1	71	1824/06	subbulakshmi	60	F	3	6.2	123	222	234	201	58	136	40	yes		110	70	1.52	58	25	no	no	no	no
78	1	74	1127/09	appa rao	68	M	25	6.3	102	180	189	148	53	106	30	nil	29	170	90	1.66	61	22	yes	no	no	no
79	1	77	1090798	vaithialingam	60	M	3	7.9	112	256	173	182	61	76	36	nil	68	132	84	1.62	58	22	no	no	no	no
80	1	78	644/10	mariyadas	45	M	3	5.6	162	314	198	167	59	106	33	nil	17	98	62	1.62	60	22	no	no	yes	yes
81	1	79	227/03	amanullah	62	M	8	13.6	92	262	179	192	61	80	38	nil	88	178	88	1.58	50	20	yes	no	no	no
82	1	80	115/09	sannasi	60	M	8	8.8	116	208	189	217	59	87	43	yes		128	72	1.66	60	21	yes	yes	no	no
83	1	82	571/07	sivakumar	55	M	3	6.5	122	173	169	178	55	78	36	yes		182	114	1.65	57	20	no	no	no	no
84	1	83	1897/09	swaminathan	73	M	3	7.9	152	242	188	217	61	84	43	nil	52	160	108	1.61	60	23	yes	no	no	no
85	1	84	2376/08	govidarajan	64	M	3	9.7	176	240	173	146	51	93	29	nil	67	140	70	1.64	65	24	no	no	no	no
86	1	85	1705/03	rajapillai	48	M	15	12.1	102	206	168	137	49	92	27	nil	46	170	100	1.73	68	22	yes	no	no	yes
87	1	86	1228/07	gopal	75	M	5	5.8	104	168	168	131	47	95	26	nil	24	130	90	1.48	45	20	no	no	no	no
88	1	87	2230/09	sundaraj	50	M	4	7.6	150	316	207	194	55	113	39	nil	39	162	106	1.58	54	21	yes	yes	no	no
89	1	88	1101372	selvi	57	F	10	10.7	132	268	171	203	56	74	41	nil	71	136	90	1.53	55	23	no	no	no	no
90	1	89	1100590	uma	48	F	15	8.6	140	277	207	186	55	115	37	nil	41	140	90	1.39	45	23	yes	no	yes	no
91	1	90	1894/09	ganesan	68	M	10	6.1	96	136	247	178	61	150	36	nil	22	156	100	1.62	65	24	yes	no	no	no
92	1	91	1488/06	ukham	54	M	4	7.6	124	254	216	162	54	130	32	nil	48	120	80	1.62	49	18	no	no	no	no
93	1	92	1739/04	dharmaraj	57	M	8	8.1	128	266	213	198	57	116	40	nil	41	124	76	1.75	62	20	no	no	no	no

MASTER CHART

94	1	93	648/03	arumugam	55	M	4	5.9	133	297	187	162	54	101	32	nil	23	152	104	1.53	65	27	yes	yes	no	yes
95	1	94	1049/08	palanisamy	51	M	5	15.7	112	224	243	102	57	146	40	nil	62	148	96	1.61	52	20	yes	no	no	no
96	1	95	1802/10	kumar	41	M	3	6.1	102	210	181	157	49	101	31	nil	27	110	70	1.67	70	25	no	no	yes	no
97	1	96	2511/07	govindaraju	60	M	4	6.1	177	326	247	169	53	161	33	nil	22	120	76	1.63	66	24	no	no	no	no
98	1	98	1141/10	kamaraj	45	M	4	8.2	167	314	237	196	58	140	39	nil	48	118	74	1.79	73	22	no	no	no	no
99	1	99	1492/10	thangaraj	60	M	3	6.1	237	326	187	163	54	101	32	nil	27	120	78	1.71	68	23	no	no	no	no
100	1	100	1103989	muthukumaran	49	M	5	10.8	124	285	241	198	57	144	40	nil	46	130	80	1.65	55	20	no	no	no	no